

VIRAL POLYMERASE INHIBITORS

RELATED APPLICATIONS

This application claims benefit of U.S. Serial No. USSN 61/015123, filed December
5 19, 2007, which is herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for the
treatment of hepatitis C virus (HCV) infection. In particular, the present invention
10 provides novel inhibitors of the hepatitis C virus NS5B polymerase, pharmaceutical
compositions containing such compounds and methods for using these compounds
in the treatment of HCV infection.

BACKGROUND OF THE INVENTION

15 It is estimated that at least 170 million persons worldwide are infected with the
hepatitis C virus (HCV). Acute HCV infection progresses to chronic infection in a
high number of cases, and, in some infected individuals, chronic infection leads to
serious liver diseases such as cirrhosis and hepatocellular carcinoma.

20 Currently, standard treatment of chronic hepatitis C infection involves administration
of pegylated interferon-alpha in combination with ribavirin. However, this therapy is
not effective in reducing HCV RNA to undetectable levels in many infected patients
and is associated with often intolerable side effects such as fever and other
influenza-like symptoms, depression, thrombocytopenia and hemolytic anemia.

25 Furthermore, some HCV-infected patients have co-existing conditions which
contraindicate this treatment.

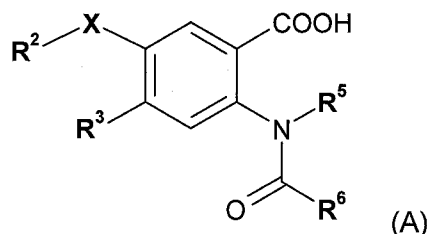
Therefore, a need exists for alternative treatments for hepatitis C viral infection. One
possible strategy to address this need is the development of effective antiviral
30 agents which inactivate viral or host cell factors which are essential for viral
replication.

HCV is an enveloped positive strand RNA virus in the genus *Hepacivirus* in the
Flaviviridae family. The single strand HCV RNA genome is approximately 9500
35 nucleotides in length and has a single open reading frame (ORF), flanked by 5' and

3' non-translated regions. The HCV 5' non-translated region is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation. The open reading frame encodes a single large polyprotein of about 3000 amino acids which is cleaved at multiple sites by cellular and viral proteases to produce the mature structural and non-structural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins. The viral NS2/3 protease cleaves at the NS2-NS3 junction; while the viral NS3 protease mediates the cleavages downstream of NS3, at the NS3-NS4A, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B cleavage sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. The NS4A protein acts as a cofactor for the NS3 protease and may also assist in the membrane localization of NS3 and other viral replicase components. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The NS5B protein is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity.

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in non-human mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics. It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051).

WO 2007/087717 discloses compounds of the general formula (A):

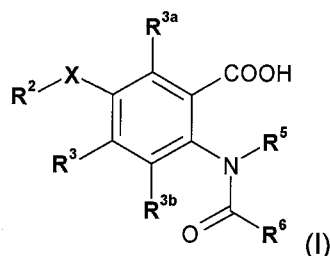


wherein R^2 is an optionally substituted aryl and R^6 is an optionally substituted (C_5 - γ)cycloalkyl or aryl which are useful for the treatment of Hepatitis C virus infections.

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against HCV polymerase. In particular compounds according to this invention inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV, especially the enzyme NS5B encoded by HCV. A further advantage of compounds provided by this invention is their low to very low or even non-significant activity against other polymerases. Further objects of this invention arise for the one skilled in the art from the following description and the examples.

One aspect of the invention provides compounds of formula (I):



wherein:

X is selected from O and S;

R^2 is **Het** or aryl, optionally substituted with 1 to 5 R^{20} substituents, wherein R^{20} in each case is independently selected from:

a) halo, cyano or nitro;

b) R^7 , $-C(=O)-R^7$, $-C(=O)-O-R^7$, $-O-R^7$, $-S-R^7$, $-SO-R^7$, $-SO_2-R^7$,

$-(C_{1-6})alkylene-R^7$, $-(C_{1-6})alkylene-C(=O)-R^7$,

$-(C_{1-6})alkylene-C(=O)-O-R^7$, $-(C_{1-6})alkylene-O-R^7$, $-(C_{1-6})alkylene-S-R^7$, $-(C_{1-6})alkylene-SO-R^7$ or $-(C_{1-6})alkylene-SO_2-R^7$;

wherein R^7 is in each instance independently selected from H,

$(C_{1-6})alkyl$, $(C_{2-6})alkenyl$, $(C_{2-6})alkynyl$, $(C_{1-6})haloalkyl$, $(C_{3-7})cycloalkyl$,

$(C_{3-7})cycloalkyl-(C_{1-6})alkyl$, aryl and **Het**;

wherein the $(C_{1-6})alkyl$, $(C_{2-6})alkenyl$, $(C_{2-6})alkynyl$, $(C_{1-6})haloalkyl$,

$(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-6})alkyl$, and $(C_{1-6})alkylene$ are

optionally substituted with 1 or 2 substituents each independently

selected from $-OH$, $-(C_{1-6})alkyl$ (optionally substituted with

$-O-(C_{1-6})alkyl$), halo, $-(C_{1-6})haloalkyl$, $(C_{3-7})cycloalkyl$, $-O-(C_{1-6})alkyl$,

cyano, $COOH$, $-NH_2$, $-NH(C_{1-4})alkyl$, $-NH(C_{3-7})cycloalkyl$,

-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂, aryl, -(C₁₋₆)alkyl-aryl, **Het**,
-(C₁₋₆)alkyl-**Het**; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3
substituents each independently selected from:

- 5 i) halo, cyano, oxo, thioxo, imino, -OH, -O-(C₁₋₆)alkyl,
-O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,
-C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,
-C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
-C(=O)-NH(C₃₋₇)cycloalkyl,
10 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
-N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
-O-(C₁₋₆)alkyl; and
15 iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
substituted with halo or (C₁₋₆)alkyl; and

c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹,
-(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹,
-(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹;

20 wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2
substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo,
-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂,
-NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and
-N((C₁₋₄)alkyl)₂;

25 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
(C₃₋₇)cycloalkyl; and

R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl,
-(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and
-C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;

30 or R⁸ and R⁹, together with the N to which they are attached,
are linked to form a 4- to 7-membered heterocycle optionally further
containing 1 to 3 heteroatoms each independently selected from N, O
and S, wherein each S heteroatom may, independently and where
possible, exist in an oxidized state such that it is further bonded to
35 one or two oxygen atoms to form the groups SO or SO₂;

wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂,
 5 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

R³, **R^{3a}** and **R^{3b}** are selected from H, halo, CN, (C₁₋₄)alkyl, -OH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;

10 **R⁵** is **R⁵¹** mono-, di-, or tri-substituted with O-**R⁵²**,
 wherein **R⁵¹** is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, each **R⁵¹** being optionally substituted with (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; and
R⁵² is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, said aryl and **Het** being optionally substituted with
 15 (C₁₋₆)alkyl or O-(C₁₋₆)alkyl;

R⁶ is (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**; being optionally substituted with 1 to 5 substituents each independently selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and -N(**R⁸**)(**R⁹**); wherein **R⁸** and **R⁹** are as defined above; and
 20 **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1

to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where
 25 possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;
 30 or a salt or ester thereof.

Another aspect of this invention provides a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, as a medicament.

Still another aspect of this invention provides a pharmaceutical composition

comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof; and one or more pharmaceutically acceptable carriers.

- 5 According to an embodiment of this aspect, the pharmaceutical composition according to this invention additionally comprises at least one other antiviral agent.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of a hepatitis C viral infection in a mammal having or
10 at risk of having the infection.

A further aspect of the invention involves a method of treating a hepatitis C viral infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a
15 compound of formula (I), a pharmaceutically acceptable salt or ester thereof, or a composition thereof as described hereinabove.

Another aspect of the invention involves a method of treating a hepatitis C viral infection in a mammal having or at risk of having the infection, the method
20 comprising administering to the mammal a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, and at least one other antiviral agent; or a composition thereof.

Also within the scope of this invention is the use of a compound of formula (I) as
25 described herein, or a pharmaceutically acceptable salt or ester thereof, for the treatment of a hepatitis C viral infection in a mammal having or at risk of having the infection.

Another aspect of this invention provides the use of a compound of formula (I) as
30 described herein, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for the treatment of a hepatitis C viral infection in a mammal having or at risk of having the infection.

An additional aspect of this invention refers to an article of manufacture comprising a
35 composition effective to treat a hepatitis C viral infection; and packaging material

comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound of formula (I) according to this invention or a pharmaceutically acceptable salt or ester thereof.

- 5 Still another aspect of this invention relates to a method of inhibiting the replication of hepatitis C virus comprising exposing the virus to an effective amount of the compound of formula (I), or a salt or ester thereof, under conditions where replication of hepatitis C virus is inhibited.
- 10 Further included in the scope of the invention is the use of a compound of formula (I), or a salt or ester thereof, to inhibit the replication of hepatitis C virus.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

- 15 As used herein, the following definitions apply unless otherwise noted:

The term "substituent", as used herein and unless specified otherwise, is intended to mean an atom, radical or group which may be bonded to a carbon atom, a heteroatom or any other atom which may form part of a molecule or fragment

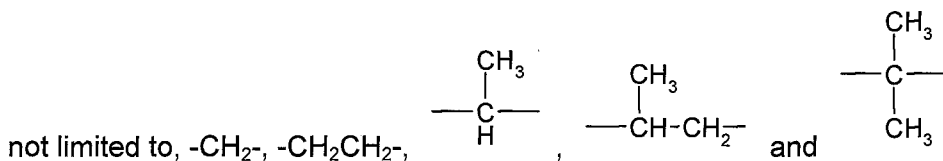
- 20 thereof, which would otherwise be bonded to at least one hydrogen atom.

Substituents contemplated in the context of a specific molecule or fragment thereof are those which give rise to chemically stable compounds, such as are recognized by those skilled in the art.

- 25 The term "(C_{1-n})alkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain alkyl radicals containing from 1 to n carbon atoms, and includes, but is not limited to, methyl, ethyl, propyl (*n*-propyl), butyl (*n*-butyl), 1-methylethyl (*iso*-propyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl),
- 30 pentyl and hexyl. The abbreviation Me denotes a methyl group; Et denotes an ethyl group, Pr denotes a propyl group, iPr denotes a 1-methylethyl group, Bu denotes a butyl group and tBu denotes a 1,1-dimethylethyl group.

- The term "(C_{1-n})alkylene" as used herein, wherein n is an integer, either alone or in
- 35 combination with another radical, is intended to mean acyclic, straight or branched

chain divalent alkyl radicals containing from 1 to n carbon atoms and includes, but is



The term “(C_{2-n})alkenyl”, as used herein, wherein n is an integer, either alone or in
 5 combination with another radical, is intended to mean an unsaturated, acyclic
 straight or branched chain radical containing two to n carbon atoms, at least two of
 which are bonded to each other by a double bond. Examples of such radicals
 include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl.
 Unless specified otherwise, the term “(C_{2-n})alkenyl” is understood to encompass
 10 individual stereoisomers where possible, including but not limited to (E) and (Z)
 isomers, and mixtures thereof. When a (C_{2-n}) alkenyl group is substituted, it is
 understood to be substituted on any carbon atom thereof which would otherwise
 bear a hydrogen atom, unless specified otherwise, such that the substitution would
 give rise to a chemically stable compound, such as are recognized by those skilled in
 15 the art.

The term “(C_{2-n})alkynyl”, as used herein, wherein n is an integer, either alone or in
 combination with another radical, is intended to mean an unsaturated, acyclic
 straight or branched chain radical containing two to n carbon atoms, at least two of
 20 which are bonded to each other by a triple bond. Examples of such radicals include,
 but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butyne. When a
 (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon
 atom thereof which would otherwise bear a hydrogen atom, unless specified
 otherwise, such that the substitution would give rise to a chemically stable
 25 compound, such as are recognized by those skilled in the art.

The term “(C_{3-m})cycloalkyl” as used herein, wherein m is an integer, either alone or in
 combination with another radical, is intended to mean a cycloalkyl substituent
 containing from 3 to m carbon atoms and includes, but is not limited to, cyclopropyl,
 30 cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term “(C_{3-m})cycloalkyl-(C_{1-n})alkyl-” as used herein, wherein n and m are both

integers, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a cycloalkyl radical containing from 3 to m carbon atoms as defined above, and includes, but is not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclobutylethyl, 2-cyclobutylethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. When a (C_{3-m})cycloalkyl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the cycloalkyl or the alkyl portion thereof or both, unless specified otherwise.

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The term "aryl" as used herein, either alone or in combination with another radical, is intended to mean a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl and dihydronaphthyl.

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The term "aryl-(C_{1-n})alkyl-" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with an aryl radical as defined above. Examples of aryl-(C_{1-n})alkyl- include, but are not limited to, phenylmethyl (benzyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. When an aryl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the aryl or the alkyl portion thereof or both, unless specified otherwise.

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The term "Het" as used herein, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen

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atoms to form the groups SO or SO₂, unless specified otherwise. When a **Het** group is substituted, it is understood that substituents may be attached to any carbon atom or heteroatom thereof which would otherwise bear a hydrogen atom, unless specified otherwise.

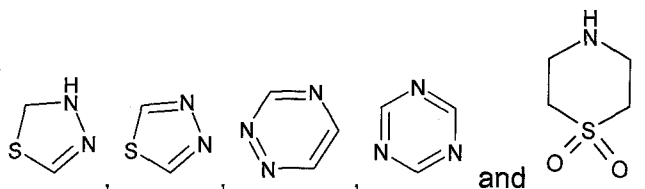
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The term "**Het**-(C_{1-n})alkyl-" as used herein and unless specified otherwise, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a **Het** substituent as defined above. Examples of **Het**-(C_{1-n})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidylethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. When a **Het**-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the **Het** or the alkyl portion thereof or both, unless specified otherwise.

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The term "heteroatom" as used herein is intended to mean O, S or N.

The term "heterocycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle containing from 1 to 4 heteroatoms each independently selected from O, N and S; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heterocycles include, but are not limited to, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, oxazolidine, pyrrole, thiophene, furan, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, tetrazole, piperidine, piperazine, azepine, diazepine, pyran, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide, pyridazine, pyrazine, pyrimidine, and the following heterocycles:

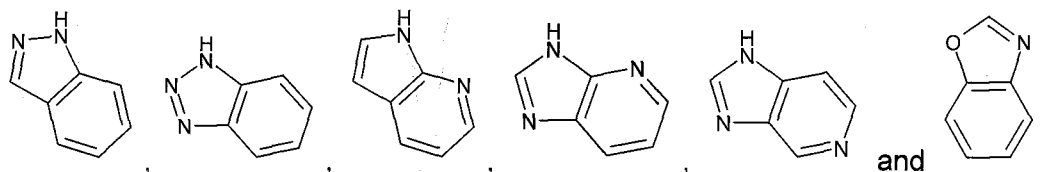


and saturated, unsaturated and aromatic derivatives thereof.

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The term "heteropolycycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a heterocycle as

defined above fused to one or more other cycle, including a carbocycle, a heterocycle or any other cycle; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heteropolycycles include, but are not limited to, indole, isoindole, benzimidazole, benzothiophene, benzofuran, benzodioxole, benzothiazole, quinoline, isoquinoline, naphthyridine, and the following heteropolycycles:



and saturated, unsaturated and aromatic derivatives thereof.

- 10 The term "halo" as used herein is intended to mean a halogen substituent selected from fluoro, chloro, bromo or iodo.

- The term "(C_{1-n})haloalkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above wherein one or more hydrogen atoms are each replaced by a halo substituent. Examples of (C_{1-n})haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

- 20 The terms "-O-(C_{1-n})alkyl" or "(C_{1-n})alkoxy" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an oxygen atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -O-(C_{1-n})alkyl include but are not limited to methoxy (CH₃O-), ethoxy (CH₃CH₂O-), propoxy (CH₃CH₂CH₂O-), 1-methylethoxy (*iso*-propoxy; (CH₃)₂CH-O-) and 1,1-dimethylethoxy (*tert*-butoxy; (CH₃)₃C-O-). When an -O-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof.

- 30 The terms "-S-(C_{1-n})alkyl" or "(C_{1-n})alkylthio" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an sulfur atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -S-(C_{1-n})alkyl include but are not limited to methylthio

(CH₃S-), ethylthio (CH₃CH₂S-), propylthio (CH₃CH₂CH₂S-), 1-methylethylthio (isopropylthio; (CH₃)₂CH-S-) and 1,1-dimethylethylthio (*tert*-butylthio; (CH₃)₃C-S-).

When -S-(C_{1-n})alkyl radical, or an oxidized derivative thereof, such as an -SO-(C_{1-n})alkyl radical or an -SO₂-(C_{1-n})alkyl radical, is substituted, each is
5 understood to be substituted on the (C_{1-n})alkyl portion thereof.

The term "oxo" as used herein is intended to mean an oxygen atom attached to a carbon atom as a substituent by a double bond (=O).

10 The term "thioxo" as used herein is intended to mean a sulfur atom attached to a carbon atom as a substituent by a double bond (=S).

The term "imino" as used herein is intended to mean a NH group attached to a carbon atom as a substituent by a double bond (=NH).

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The term "cyano" or "CN" as used herein is intended to mean a nitrogen atom attached to a carbon atom by a triple bond (C≡N).

The term "COOH" as used herein is intended to mean a carboxyl group (-C(=O)-OH).

20 It is well known to one skilled in the art that carboxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents contemplated in this invention include, but are not limited to, esters, amides, imides, boronic acids, phosphonic acids, phosphoric acids, tetrazoles, triazoles, N-acylsulfamides (RCONHSO₂NR₂), and N-acylsulfonamides (RCONHSO₂R).

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The term "functional group equivalent" as used herein is intended to mean an atom or group that may replace another atom or group which has similar electronic, hybridization or bonding properties.

30 The term "protecting group" as used herein is intended to mean protecting groups that can be used during synthetic transformation, including but not limited to examples which are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981), and more recent editions thereof, herein incorporated by reference.

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The following designation  is used in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

5 The term "salt thereof" as used herein is intended to mean any acid and/or base addition salt of a compound according to the invention, including but not limited to a pharmaceutically acceptable salt thereof.

10 The term "pharmaceutically acceptable salt" as used herein is intended to mean a salt of a compound according to the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts.

15 Lists of suitable salts are found in, for example, S.M. Berge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, herein incorporated by reference.

The term "pharmaceutically-acceptable acid addition salt" as used herein is intended to mean those salts which retain the biological effectiveness and properties of the

20 free bases and which are not biologically or otherwise undesirable, formed with inorganic acids including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid and the like, and organic acids including but not limited to acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid,

25 camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid,

30 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid and the like.

The term "pharmaceutically-acceptable base addition salt" as used herein is intended to mean those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases including but not limited to ammonia or the hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include but are not limited to salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, N,N'-dibenzylethylenediamine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "ester thereof" as used herein is intended to mean any ester of a compound according to the invention in which any of the -COOH substituents of the molecule is replaced by a -COOR substituent, in which the **R** moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, each of which being optionally further substituted. The term "ester thereof" includes but is not limited to pharmaceutically acceptable esters thereof.

The term "pharmaceutically acceptable ester" as used herein is intended to mean esters of the compound according to the invention in which any of the COOH substituents of the molecule are replaced by a -COOR substituent, in which the **R** moiety of the ester is selected from alkyl (including, but not limited to, methyl, ethyl,

propyl, 1-methylethyl, 1,1-dimethylethyl, butyl); alkoxyalkyl (including, but not limited to methoxymethyl); acyloxyalkyl (including, but not limited to acetoxymethyl); arylalkyl (including, but not limited to, benzyl); aryloxyalkyl (including, but not limited to, phenoxymethyl); and aryl (including, but not limited to phenyl) optionally substituted with halogen, (C₁₋₄)alkyl or (C₁₋₄)alkoxy. Other suitable esters can be found in Design of Prodrugs, Bundgaard, H. Ed. Elsevier (1985), herein incorporated by reference. Such pharmaceutically acceptable esters are usually hydrolyzed *in vivo* when injected into a mammal and transformed into the acid form of the compound according to the invention. With regard to the esters described above, unless otherwise specified, any alkyl moiety present preferably contains 1 to 16 carbon atoms, more preferably 1 to 6 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group. In particular the esters may be a (C₁₋₁₆)alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted with at least one halogen, (C₁₋₆)alkyl, (C₁₋₆)alkoxy, nitro or trifluoromethyl.

The term "mammal" as used herein is intended to encompass humans, as well as non-human mammals which are susceptible to infection by hepatitis C virus. Non-human mammals include but are not limited to domestic animals, such as cows, pigs, horses, dogs, cats, rabbits, rats and mice, and non-domestic animals.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of the hepatitis C disease and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood.

The term "antiviral agent" as used herein is intended to mean an agent that is effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal.

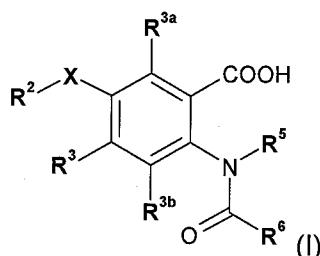
The term "therapeutically effective amount" means an amount of a compound

according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

15

Preferred embodiments

In the following preferred embodiments, groups and substituents of the compounds of formula (I):



20 are described in detail.

X:

X-A: In one embodiment, X is O.

X-B: In another embodiment, X is S.

25 **X-C:** In another embodiment, X is O or S.

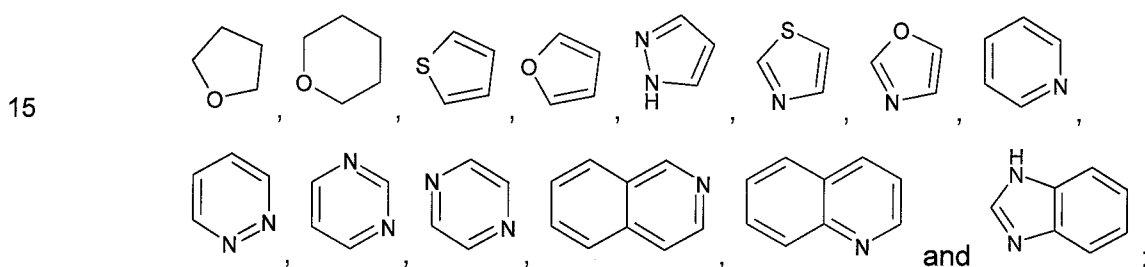
Any and each individual definition of X as set out herein may be combined with any and each individual definition of R^2 , R^{20} , R^3 , R^{3a} , R^{3b} , R^5 and R^6 as set out herein.

R²:

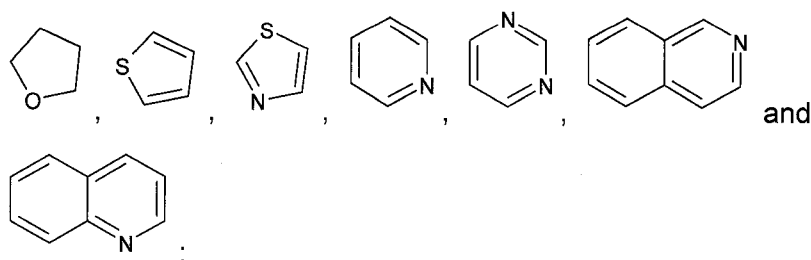
R²-A: In one embodiment, **R²** is **Het** or aryl, optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** is as defined herein.

- R²-B:** In another embodiment, **R²** is **Het** wherein **Het** is a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N and S, or a 9- or 10-membered bicyclic heteropolycycle containing 1 to 3 heteroatoms each independently selected from O, N and S; wherein **Het** is optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** is as defined herein.
- R²-C:** In another embodiment, **R²** is **Het** wherein **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms; wherein **Het** is optionally substituted with 1 to 3 **R²⁰** substituents, wherein **R²⁰** is as defined herein.

R²-D: In another embodiment, **R²** is **Het** selected from the following formulas:



- R²-E:** In another embodiment, **R²** is **Het** selected from the following formulas:

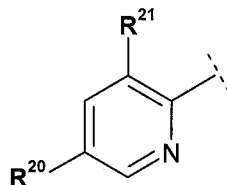


- R²-F:** In another embodiment, **R²** is **Het** of the formula:



wherein **Het** is optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20} is as defined herein.

R²-G: In another embodiment, R^2 is of the formula:



5 wherein R^{21} is as defined:

R²¹-A: In this embodiment, R^{21} is selected from H, halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl and $-O-(C_{1-6})$ haloalkyl.

R²¹-B: In this embodiment, R^{21} is selected from H, Cl, Br, CH_3 , CHF_2 , CF_3 , cyclopropyl, cyclobutyl and $-OCF_3$.

10 **R²¹-C:** In this embodiment, R^{21} is H, CHF_2 , CF_3 or cyclopropyl.

R²¹-D: In this embodiment, R^{21} is H or CF_3 .

R²¹-E: In this embodiment, R^{21} is CHF_2 or CF_3 .

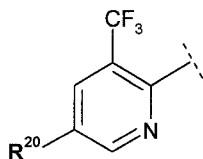
R²¹-F: In this embodiment, R^{21} is CF_3 ;

and R^{20} is as defined herein.

15

Any and each individual definition of R^{21} as set out herein may be combined with any and each individual definition of X , R^{20} , R^3 , R^{3a} , R^{3b} , R^5 and R^6 as set out herein.

R²-H: In another embodiment, R^2 is a group of the formula:



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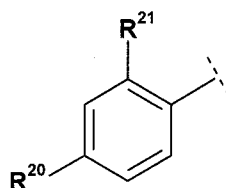
wherein R^{20} is as defined herein.

R²-I: In another embodiment, R^2 is naphthyl or phenyl, the phenyl being optionally substituted with 1 to 3 R^{20} wherein R^{20} is as defined herein.

R²-J: In yet another embodiment, R^2 is phenyl optionally substituted with 1 to 3 R^{20} wherein R^{20} is as defined herein.

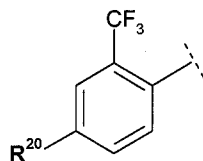
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R²-K: In an alternative embodiment, R^2 is a group of formula:



wherein R^{21} and R^{20} are as defined herein.

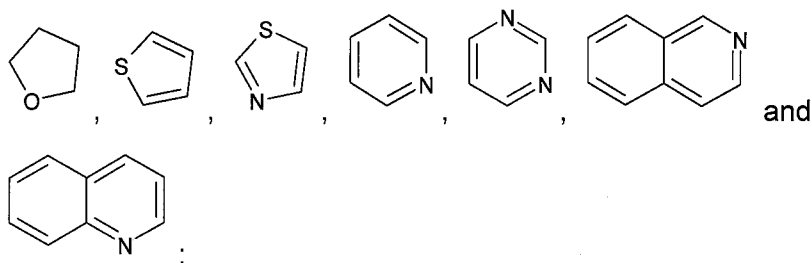
R²-L: In another embodiment, R^2 is a group of the formula:



5 wherein R^{20} is as defined herein.

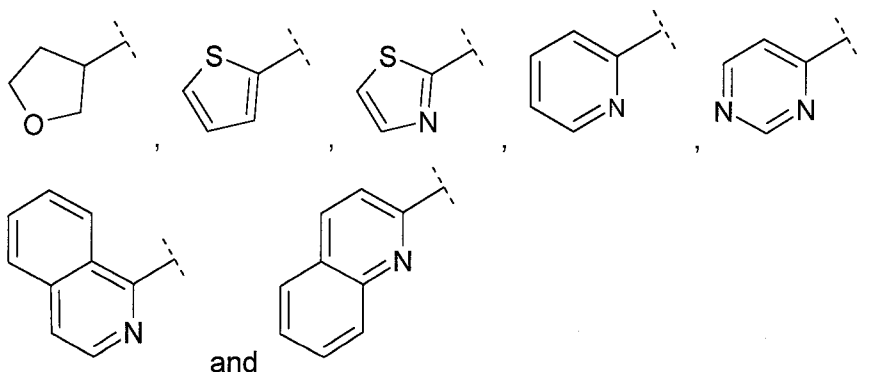
R²-M: In another embodiment, R^2 is phenyl or **Het**, all being optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20} is as defined herein; and **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms.

10 **R²-N:** In another embodiment, R^2 is phenyl or **Het** wherein **Het** is selected from the following formulas:



15 wherein R^2 is optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20} is as defined herein.

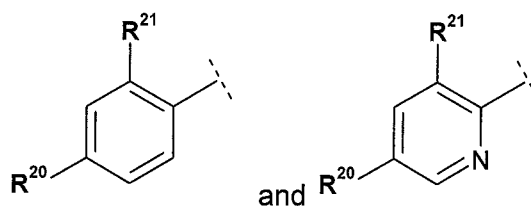
R²-O: In another embodiment, R^2 is phenyl or **Het** wherein **Het** is selected from the following formulas:



20 wherein R^2 is optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20}

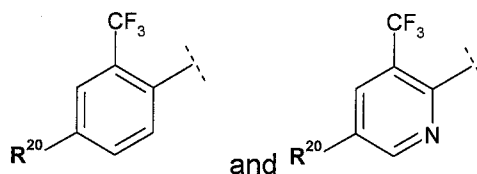
is as defined herein.

R²-P: In yet another alternative embodiment, **R²** is selected from the group:



wherein **R²¹** and **R²⁰** are as defined herein.

5 **R²-Q:** In yet another alternative embodiment, **R²** is selected from the group:



wherein **R²⁰** is as defined herein.

Any and each individual definition of **R²** as set out herein may be combined with any
 10 and each individual definition of **X**, **R²⁰**, **R³**, **R^{3a}**, **R^{3b}**, **R⁵** and **R⁶** as set out herein.

R²⁰-A:

R²⁰-A: In one embodiment, **R²⁰** is selected from:

- a) halo, cyano or nitro;
- 15 b) **R⁷**, -C(=O)-**R⁷**, -C(=O)-O-**R⁷**, -O-**R⁷**, -S-**R⁷**, -SO-**R⁷**, -SO₂-**R⁷**,
 -(C₁₋₆)alkylene-**R⁷**, -(C₁₋₆)alkylene-C(=O)-**R⁷**,
 -(C₁₋₆)alkylene-C(=O)-O-**R⁷**, -(C₁₋₆)alkylene-O-**R⁷**, -(C₁₋₆)alkylene-S-**R⁷**,
 -(C₁₋₆)alkylene-SO-**R⁷** or -(C₁₋₆)alkylene-SO₂-**R⁷**;
 wherein **R⁷** is in each instance independently selected from H,
 20 (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl,
 (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, aryl and **Het**;
 wherein the (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl,
 (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, and (C₁₋₆)alkylene are
 optionally substituted with 1 or 2 substituents each independently
 25 selected from -OH, -(C₁₋₆)alkyl optionally substituted with
 -O-(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl,
 cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂, aryl, -(C₁₋₆)alkyl-aryl, **Het**,

-(C₁₋₆)alkyl-Het; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, cyano, oxo, thioxo, imino, -OH, -O-(C₁₋₆)alkyl,

-O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,

-C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,

-C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,

-C(=O)-NH(C₃₋₇)cycloalkyl,

-C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,

-N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,

-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;

ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or -O-(C₁₋₆)alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo or (C₁₋₆)alkyl; and

c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹,

-(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹,

-(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹;

wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2

substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;

R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and

R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;

or R⁸ and R⁹, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

wherein the heterocycle is optionally substituted with 1 to 3

substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl.

5

R²⁰-B: In another embodiment, **R²⁰** is selected from:

b) **R⁷**, -C(=O)-**R⁷**, -C(=O)-O-**R⁷**, -(C₁₋₆)alkylene-**R⁷**, -(C₁₋₆)alkylene-C(=O)-**R⁷**, -(C₁₋₆)alkylene-C(=O)-O-**R⁷**, -(C₁₋₆)alkylene-O-**R⁷**, -(C₁₋₆)alkylene-S-**R⁷**;

wherein **R⁷** is in each instance independently selected from H,

10

(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, aryl and **Het**;

wherein the (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, and (C₁₋₆)alkylene are optionally substituted with 1 or 2 substituents each independently

15

selected from -OH, -(C₁₋₆)alkyl optionally substituted with -O-(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂, aryl, -(C₁₋₆)alkyl-aryl, **Het**, -(C₁₋₆)alkyl-**Het**; and

20

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, cyano, oxo, thiooxo, imino, -OH, -O-(C₁₋₆)alkyl,

-O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,

-C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,

25

-C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,

-C(=O)-NH(C₃₋₇)cycloalkyl,

-C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,

-N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,

-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;

30

ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or -O-(C₁₋₆)alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo or (C₁₋₆)alkyl; and

c) -N(**R⁸**)**R⁹**, -(C₁₋₆)alkylene-N(**R⁸**)**R⁹**, -(C₁₋₆)alkylene-C(=O)-N(**R⁸**)**R⁹**, or -(C₁₋₆)alkylene-O-C(=O)-N(**R⁸**)**R⁹**; wherein the (C₁₋₆)alkylene is

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optionally substituted with 1 or 2 substituents each independently selected from $-\text{OH}$, $-(\text{C}_{1-6})\text{alkyl}$, halo, $-(\text{C}_{1-6})\text{haloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{O}-(\text{C}_{1-6})\text{alkyl}$, cyano, COOH , $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4})\text{alkyl}$, $-\text{NH}(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{N}((\text{C}_{1-4})\text{alkyl})(\text{C}_{3-7})\text{cycloalkyl}$ and $-\text{N}((\text{C}_{1-4})\text{alkyl})_2$;

5 R^8 is in each instance independently selected from H, $(\text{C}_{1-6})\text{alkyl}$ and $(\text{C}_{3-7})\text{cycloalkyl}$; and

R^9 is defined as R^7 , wherein R^7 is as defined above;

or R^8 and R^9 , together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2 ;

10 wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{1-6})\text{haloalkyl}$, halo, oxo, $-\text{OH}$, SH, $-\text{O}(\text{C}_{1-6})\text{alkyl}$, $-\text{S}(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-6})\text{alkyl}$, $-\text{N}((\text{C}_{1-6})\text{alkyl})_2$, $-\text{NH}(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{N}((\text{C}_{1-4})\text{alkyl})(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{C}(=\text{O})(\text{C}_{1-6})\text{alkyl}$ and $-\text{NHC}(=\text{O})-(\text{C}_{1-6})\text{alkyl}$.

15 $\text{R}^{20}\text{-C}$: In another embodiment, R^{20} is selected from:

b) R^7 , $-(\text{C}_{1-6})\text{alkylene-R}^7$, $-(\text{C}_{1-6})\text{alkylene-O-R}^7$, $-(\text{C}_{1-6})\text{alkylene-S-R}^7$; wherein R^7 is in each instance independently selected from H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{1-6})\text{haloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-6})\text{alkyl}$, aryl and **Het**;

25 wherein the $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{1-6})\text{haloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}-(\text{C}_{1-6})\text{alkyl}$, and $(\text{C}_{1-6})\text{alkylene}$ are optionally substituted with 1 or 2 substituents each independently selected from $-\text{OH}$, $-(\text{C}_{1-6})\text{alkyl}$ optionally substituted with $-\text{O}-(\text{C}_{1-6})\text{alkyl}$, halo, $-(\text{C}_{1-6})\text{haloalkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{O}-(\text{C}_{1-6})\text{alkyl}$, cyano, COOH , $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4})\text{alkyl}$, $-\text{NH}(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{N}((\text{C}_{1-4})\text{alkyl})(\text{C}_{3-7})\text{cycloalkyl}$, $-\text{N}((\text{C}_{1-4})\text{alkyl})_2$, **Het**, $-(\text{C}_{1-6})\text{alkyl-Het}$; and

30 wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{haloalkyl}$, $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{C}(=\text{O})-\text{NH}(\text{C}_{1-4})\text{alkyl}$, $-\text{C}(=\text{O})-\text{N}((\text{C}_{1-4})\text{alkyl})_2$,

- C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
- 5 ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
 -O-(C₁₋₆)alkyl; and
 iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
 substituted with halo or (C₁₋₆)alkyl; and
- c) -N(R⁸)R⁹ or -(C₁₋₆)alkylene-N(R⁸)R⁹; wherein the (C₁₋₆)alkylene is
 10 optionally substituted with 1 or 2 substituents each independently
 selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl,
 -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;
 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
 15 (C₃₋₇)cycloalkyl; and
 R⁹ is defined as R⁷, wherein R⁷ is as defined above.
- R²⁰-D:** In another embodiment, R²⁰ is selected from:
- b) R⁷ or -(C₁₋₆)alkylene-R⁷
 wherein R⁷ is in each instance independently selected from H,
 20 (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, phenyl and **Het**;
 wherein each of the phenyl and **Het** are optionally substituted with 1
 to 3 substituents each independently selected from:
- i) halo, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 25 -C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl; and
 ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
 30 -O-(C₁₋₆)alkyl; and
- c) -N(R⁸)R⁹ or -(C₁₋₆)alkylene-N(R⁸)R⁹;
 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
 (C₃₋₇)cycloalkyl; and
 R⁹ is defined as R⁷, wherein R⁷ is as defined above.
- 35 **R²⁰-E:** In another embodiment, R²⁰ is selected from:

b) R^7 or $-(C_{1-6})alkylene-R^7$

wherein R^7 is in each instance independently selected from H,
 $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-6})alkyl$, phenyl and **Het**;
 wherein each of the phenyl and **Het** are optionally substituted with 1
 to 3 substituents each independently selected from:

i) halo, $(C_{3-7})cycloalkyl$, $(C_{1-6})haloalkyl$, $-C(=O)-NH_2$,

$-C(=O)-NH(C_{1-4})alkyl$, $-C(=O)-N((C_{1-4})alkyl)_2$,

$-C(=O)-NH(C_{3-7})cycloalkyl$,

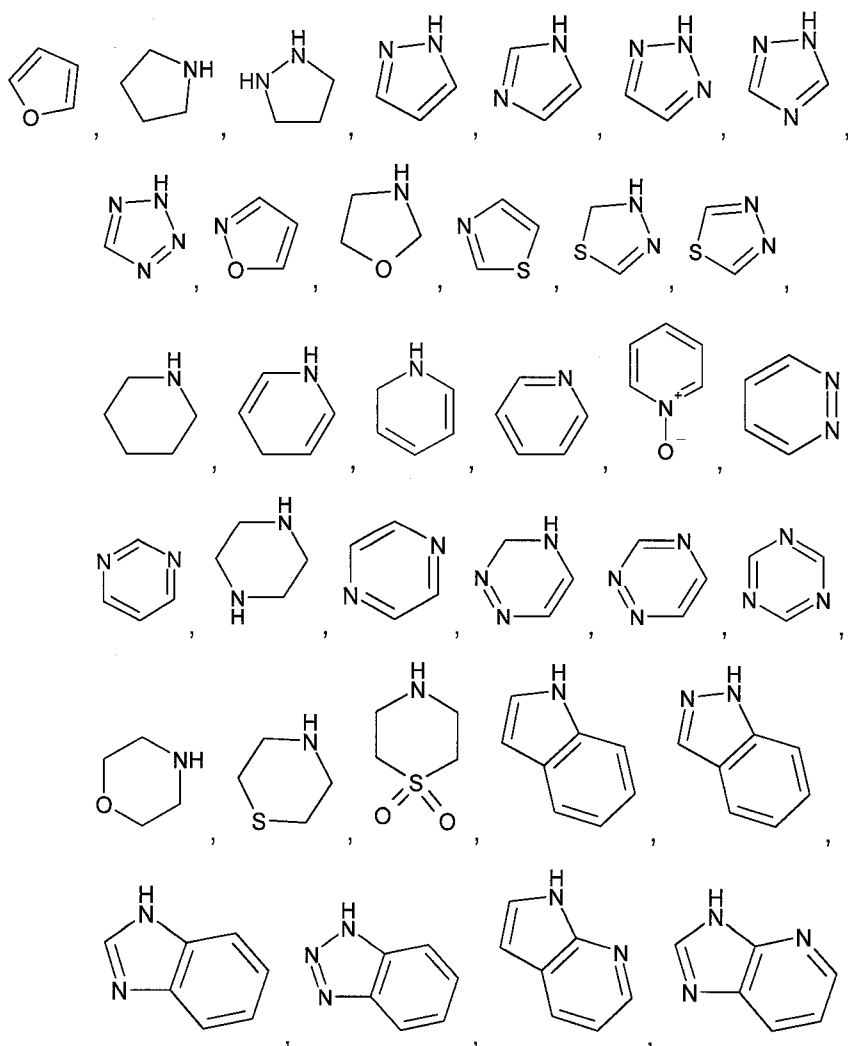
$-C(=O)-N((C_{1-4})alkyl)(C_{3-7})cycloalkyl$, $-NH_2$, $-NH(C_{1-4})alkyl$,

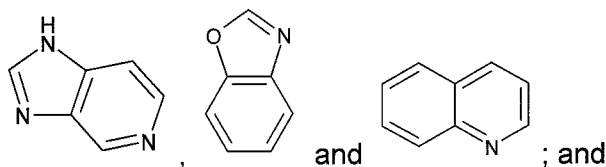
$-N((C_{1-4})alkyl)_2$, $-NH(C_{3-7})cycloalkyl$,

$-N((C_{1-4})alkyl)(C_{3-7})cycloalkyl$ or $-NH-C(=O)(C_{1-4})alkyl$; and

ii) $(C_{1-6})alkyl$ optionally substituted with $-OH$, $-O-(C_{1-6})haloalkyl$, or
 $-O-(C_{1-6})alkyl$;

wherein the **Het** is selected from:





c) $-N(R^8)R^9$ or $-(C_{1-6})\text{alkylene}-N(R^8)R^9$;

R^8 is in each instance independently selected from H, $(C_{1-6})\text{alkyl}$ and $(C_{3-7})\text{cycloalkyl}$; and

5

R^9 is defined as R^7 , wherein R^7 is as defined above.

R²⁰-F: In another embodiment, R^{20} is selected from:

b) $-(C_{1-3})\text{alkylene}-R^7$;

10

wherein R^7 is **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

15

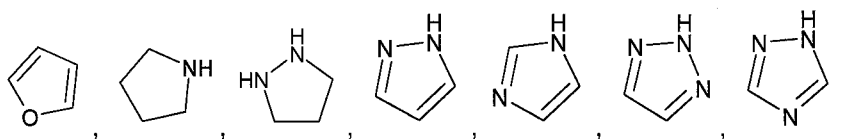
wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O- $(C_{1-6})\text{alkyl}$, -O- $(C_{1-6})\text{haloalkyl}$, $(C_{3-7})\text{cycloalkyl}$, -NH₂, -NH $(C_{1-4})\text{alkyl}$, -NH $(C_{3-7})\text{cycloalkyl}$, -N $((C_{1-4})\text{alkyl})(C_{3-7})\text{cycloalkyl}$, -N $((C_{1-4})\text{alkyl})_2$, -NH-C(=O) $(C_{1-4})\text{alkyl}$, $(C_{1-6})\text{alkyl}$ and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S.

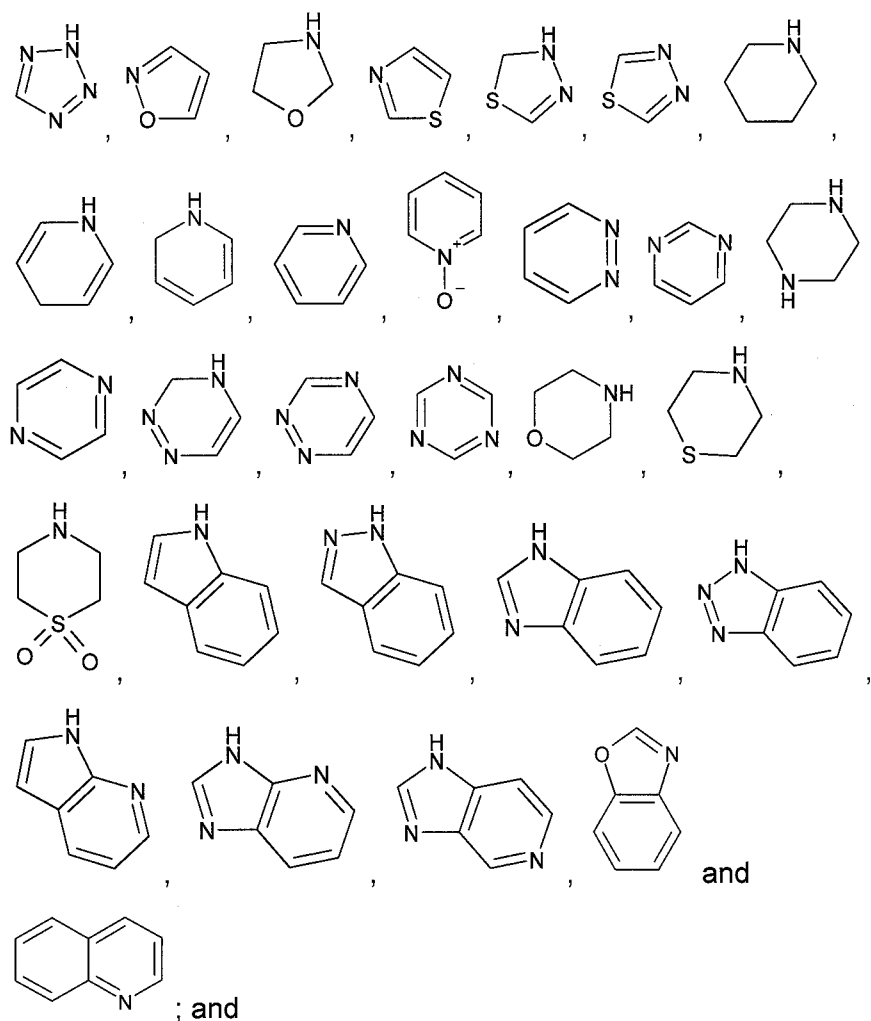
20

25 **R²⁰-G:** In another embodiment, R^{20} is selected from:

b) $-\text{CH}_2-R^7$, $-\text{CH}_2\text{CH}_2-R^7$,

wherein R^7 is **Het**; wherein the **Het** is selected from:





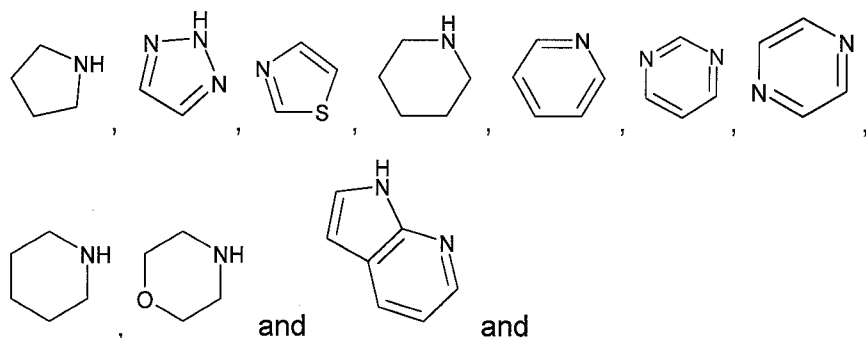
wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl and (C₁₋₆)alkyl.

10

R²⁰-H: In another embodiment, **R²⁰** is selected from:

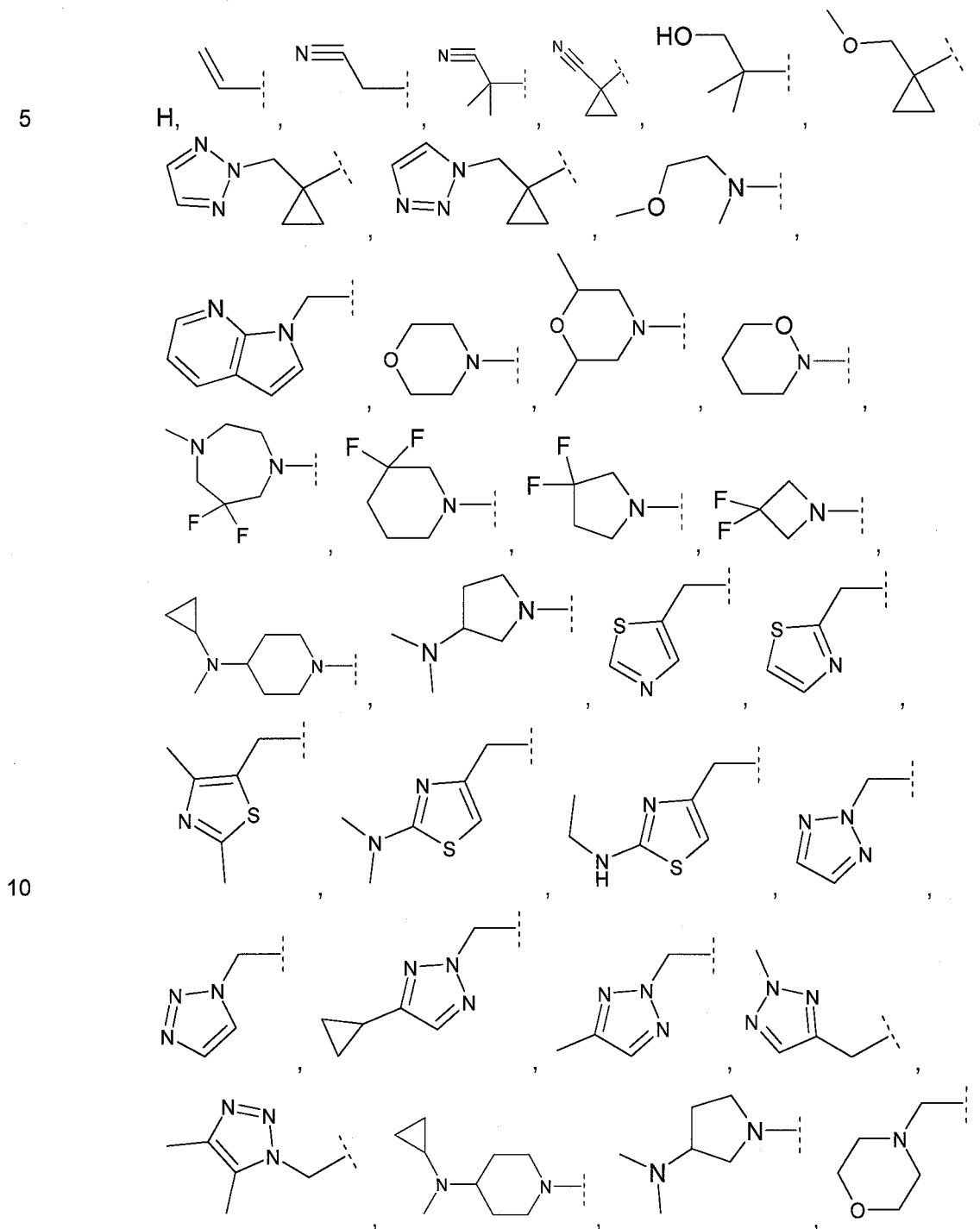
b) -CH₂-**R⁷**, -CH₂CH₂-**R⁷**,

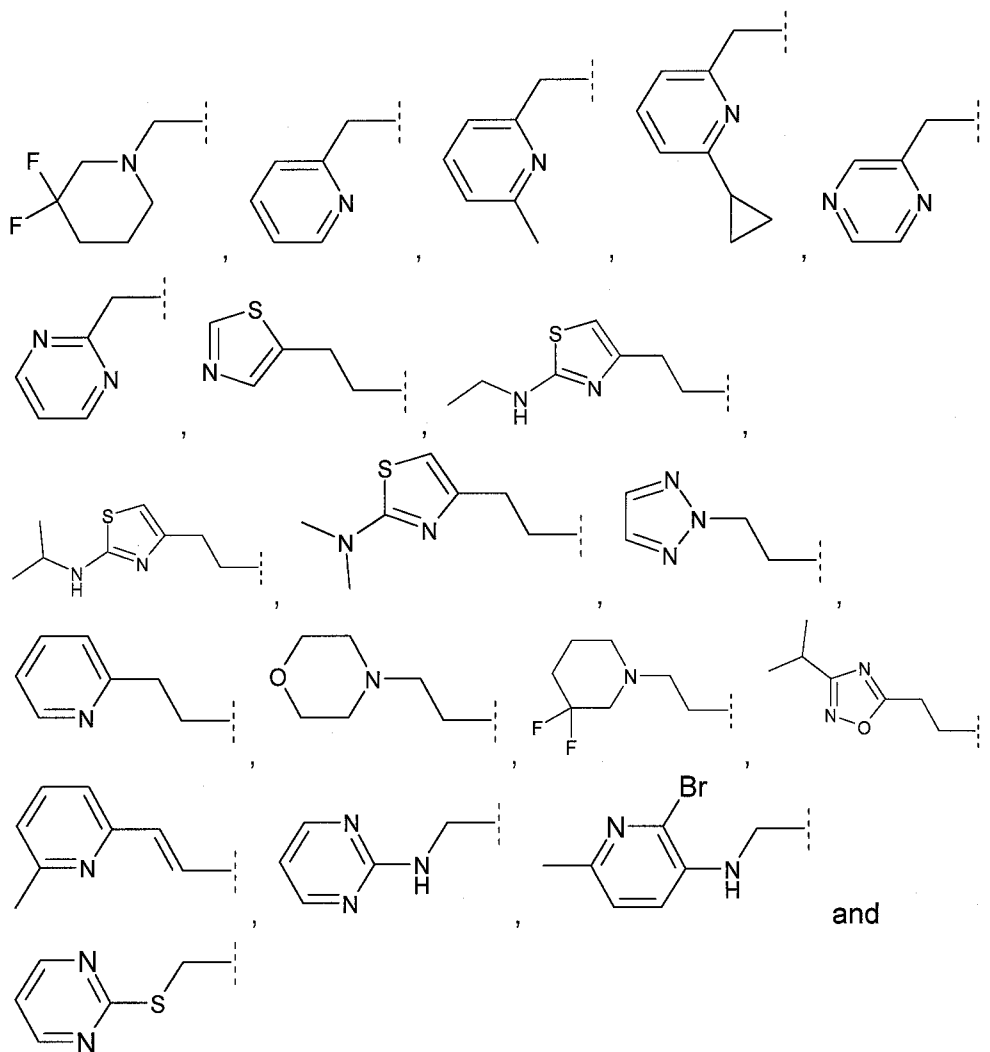
wherein **R⁷** is **Het**; wherein the **Het** is selected from:



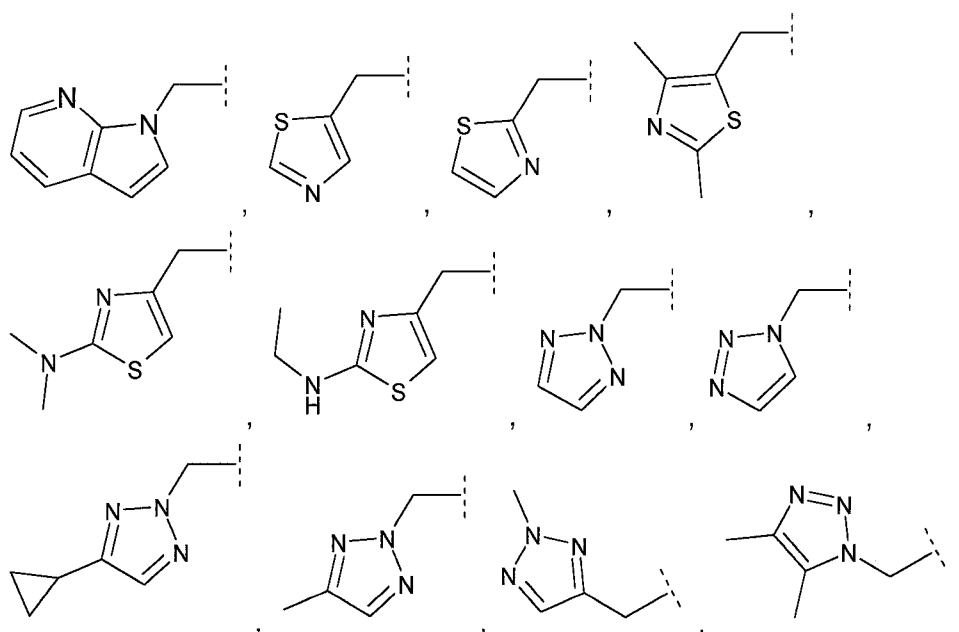
wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, $-(C_{1-6})$ alkyl, $-O-(C_{1-6})$ alkyl, $-NH_2$, $-NH(C_{1-4})$ alkyl, $-N((C_{1-4})alkyl)_2$ and (C_{1-6}) alkyl.

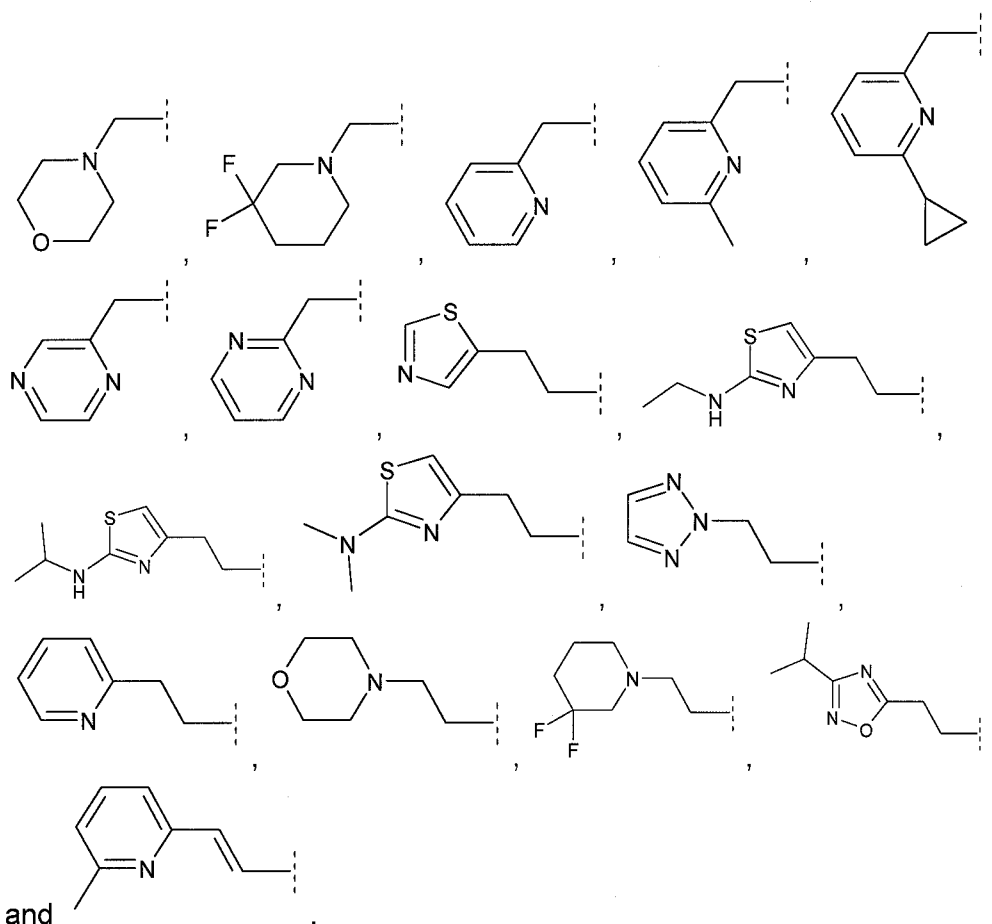
R²⁰-I: In another embodiment, R²⁰ is selected from:





R²⁰-J: In another embodiment, R²⁰ is selected from:





Any and each individual definition of R^{20} as set out herein may be combined with any and each individual definition of X , R^2 , R^3 , R^{3a} , R^{3b} , R^5 and R^6 as set out herein.

10 **R^3 :**

R^3 -A: In one embodiment, R^3 is selected from H, halo, CN, (C_{1-4}) alkyl, -OH, -O- (C_{1-4}) alkyl, -S- (C_{1-4}) alkyl, -NH₂, -NH (C_{1-4}) alkyl, -NH (C_{3-7}) cycloalkyl, -N $((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl and -N $((C_{1-4})$ alkyl)₂.

15 **R^3 -B:** In another embodiment, R^3 is selected from H, halo, CN, (C_{1-4}) alkyl, -O- (C_{1-4}) alkyl and -N $((C_{1-4})$ alkyl)₂.

R^3 -C: In another embodiment, R^3 is selected from H, halo, (C_{1-4}) alkyl and CN.

R^3 -D: In another embodiment, R^3 is selected from H, F, Cl, CH₃ and CN.

R^3 -E: In another embodiment, R^3 is selected from H, F, Cl and CH₃.

R^3 -F: In another embodiment, R^3 is selected from H, F and CH₃.

20 **R^3 -G:** In another embodiment, R^3 is H or F.

R^3 -H: In another embodiment, R^3 is H.

Any and each individual definition of R^3 as set out herein may be combined with any and each individual definition of X , R^{20} , R^2 , R^{3a} , R^{3b} , R^5 and R^6 as set out herein.

5 R^{3a} :

R^{3a} -A: In one embodiment, R^{3a} is selected from H, halo, CN, (C_{1-4}) alkyl, -OH, -O- (C_{1-4}) alkyl, -S- (C_{1-4}) alkyl, -NH₂, -NH (C_{1-4}) alkyl, -NH (C_{3-7}) cycloalkyl, -N $((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl and -N $((C_{1-4})$ alkyl)₂.

10 R^{3a} -B: In another embodiment, R^{3a} is selected from H, halo, CN, (C_{1-4}) alkyl, -O- (C_{1-4}) alkyl and -N $((C_{1-4})$ alkyl)₂.

R^{3a} -C: In another embodiment, R^{3a} is selected from H, halo, (C_{1-4}) alkyl and CN.

R^{3a} -D: In another embodiment, R^{3a} is selected from H, F, Cl, CH₃ and CN.

R^{3a} -E: In another embodiment, R^{3a} is selected from H, F, Cl and CH₃.

R^{3a} -F: In another embodiment, R^{3a} is selected from H, F and CH₃.

15 R^{3a} -G: In another embodiment, R^{3a} is H or F.

R^{3a} -H: In another embodiment, R^{3a} is H.

Any and each individual definition of R^{3a} as set out herein may be combined with any and each individual definition of X , R^{20} , R^2 , R^3 , R^{3b} , R^5 and R^6 as set out herein.

20

R^{3b} :

R^{3b} -A: In one embodiment, R^{3b} is selected from H, halo, CN, (C_{1-4}) alkyl, -OH, -O- (C_{1-4}) alkyl, -S- (C_{1-4}) alkyl, -NH₂, -NH (C_{1-4}) alkyl, -NH (C_{3-7}) cycloalkyl, -N $((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl and -N $((C_{1-4})$ alkyl)₂.

25 R^{3b} -B: In another embodiment, R^{3b} is selected from H, halo, CN, (C_{1-4}) alkyl, -O- (C_{1-4}) alkyl and -N $((C_{1-4})$ alkyl)₂.

R^{3b} -C: In another embodiment, R^{3b} is selected from H, halo, (C_{1-4}) alkyl and CN.

R^{3b} -D: In another embodiment, R^{3b} is selected from H, F, Cl, CH₃ and CN.

R^{3b} -E: In another embodiment, R^{3b} is selected from H, F, Cl and CH₃.

30 R^{3b} -F: In another embodiment, R^{3b} is selected from H, F and CH₃.

R^{3b} -G: In another embodiment, R^{3b} is H or F.

R^{3b} -H: In another embodiment, R^{3b} is H.

Any and each individual definition of R^{3b} as set out herein may be combined with any

and each individual definition of X , R^{20} , R^2 , R^3 , R^{3a} , R^5 and R^6 as set out herein.

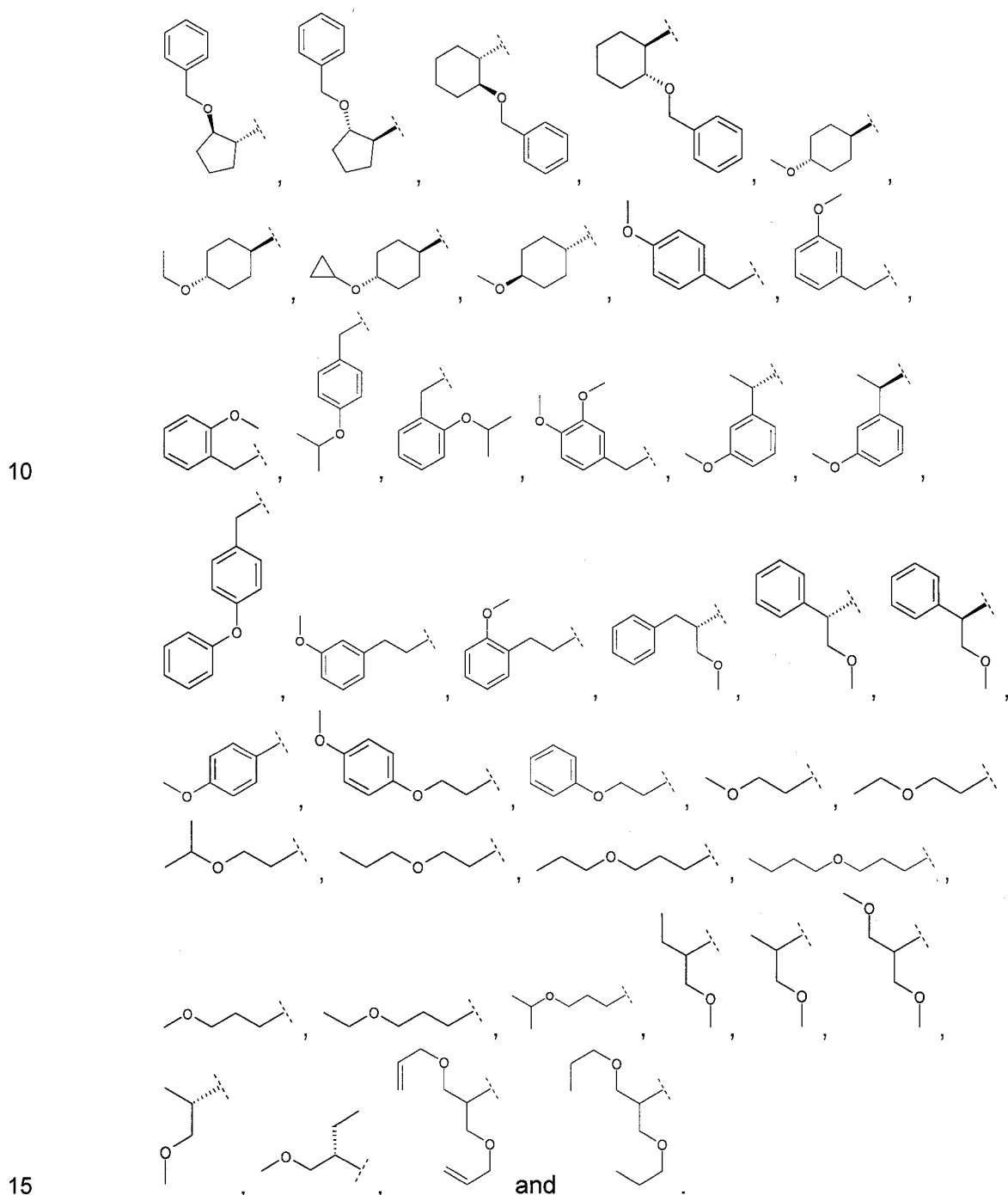
R^5 :

- R^5 -A:** In one embodiment, R^5 is R^{51} being mono-, di-, or tri-substituted with $O-R^{52}$,
 5 wherein R^{51} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, (C_{1-6}) alkyl-aryl, **Het** or (C_{1-6}) alkyl-**Het**, each R^{51} being optionally substituted with (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; and R^{52} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, (C_{1-6}) alkyl-aryl, **Het** or (C_{1-6}) alkyl-**Het**, said aryl and **Het** being optionally substituted with
 10 (C_{1-6}) alkyl or $O-(C_{1-6})$ alkyl.
- R^5 -B:** In one embodiment, R^5 is R^{51} being mono-, di-, or tri-substituted with $O-R^{52}$,
 wherein R^{51} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl or (C_{1-6}) alkyl-aryl, each R^{51} being optionally substituted with (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; and
 15 R^{52} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl or (C_{1-6}) alkyl-aryl, said aryl being optionally substituted with (C_{1-6}) alkyl or $O-(C_{1-6})$ alkyl.
- R^5 -C:** In one embodiment, R^5 is R^{51} being mono- or di-substituted with $O-R^{52}$,
 wherein R^{51} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl or (C_{1-6}) alkyl-aryl, each R^{51} being optionally substituted with (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; and
 20 R^{52} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl or (C_{1-6}) alkyl-aryl, said aryl being optionally substituted with (C_{1-6}) alkyl or $O-(C_{1-6})$ alkyl.
- R^5 -D:** In one embodiment, R^5 is R^{51} being mono- or di-substituted with $O-R^{52}$,
 wherein R^{51} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, each
 25 R^{51} being optionally substituted with (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; and R^{52} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl or (C_{1-6}) alkyl-aryl, said aryl being optionally substituted with (C_{1-6}) alkyl or $O-(C_{1-6})$ alkyl.
- R^5 -E:** In one embodiment, R^5 is R^{51} being mono- or di-substituted with $O-R^{52}$,
 30 wherein R^{51} is (C_{1-6}) alkyl, being optionally substituted with (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; and R^{52} is (C_{1-6}) alkyl, aryl or (C_{1-6}) alkyl-aryl, said aryl being optionally substituted with (C_{1-6}) alkyl or $O-(C_{1-6})$ alkyl.
- R^5 -F:** In one embodiment, R^5 is R^{51} being mono- or di-substituted with $O-R^{52}$,

wherein **R⁵¹** is (C₁₋₆)alkyl, being optionally substituted with (C₁₋₆)alkyl, and **R⁵²** is (C₁₋₆)alkyl, aryl or (C₁₋₆)alkyl-aryl, said aryl being optionally substituted with (C₁₋₆)alkyl or O-(C₁₋₆)alkyl.

R⁵-G: In one embodiment, **R⁵** is **R⁵¹** being mono- or di-substituted with O-**R⁵²**,
 5 wherein **R⁵¹** is (C₁₋₆)alkyl, being optionally substituted with (C₁₋₆)alkyl, and
 R⁵² is (C₁₋₆)alkyl.

R⁵-H: In another embodiment, R⁵ is selected from:



R⁵-I: In one embodiment, **R⁵** is **R⁵¹** being mono- or di-substituted with **O-R⁵²**,
 wherein **R⁵¹** is (C₁₋₆)alkyl, being optionally substituted with (C₁₋₆)alkyl,
 (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; and
R⁵² is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl or (C₁₋₆)alkyl-
 5 aryl, said aryl being optionally substituted with (C₁₋₆)alkyl or O-(C₁₋₆)alkyl.

Any and each individual definition of **R⁵** as set out herein may be combined with any
 and each individual definition of **X**, **R²⁰**, **R²**, **R³**, **R^{3a}**, **R^{3b}** and **R⁶** as set out herein.

10 **R⁶:**

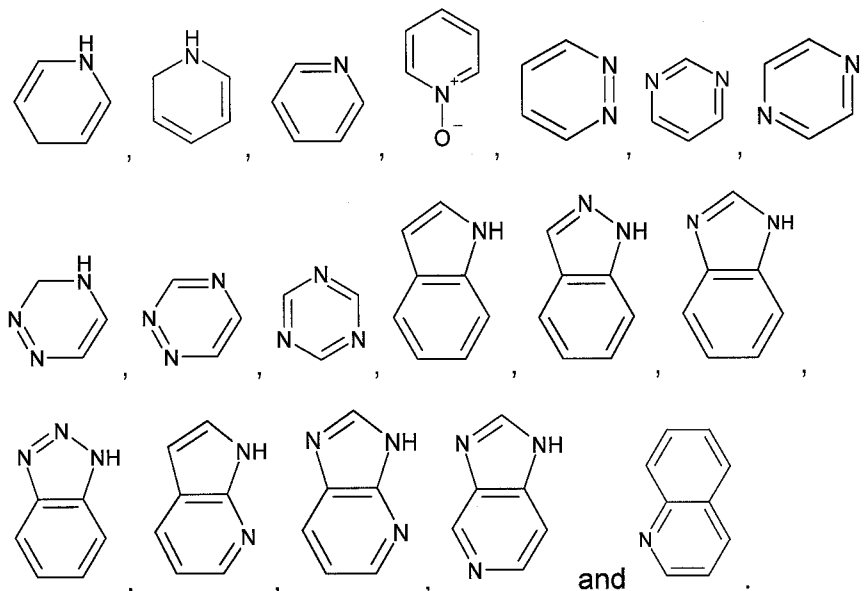
R⁶-A: In one embodiment, **R⁶** is (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl,
 (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**; being optionally substituted with 1 to 5
 substituents each independently selected from halo, (C₁₋₆)alkyl,
 (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and
 15 -N(**R⁸**)**R⁹**; wherein **R⁸** is in each instance independently selected from H, (C₁₋₆)
 alkyl and (C₃₋₇)cycloalkyl; and
R⁹ is in each instance independently selected from **R⁷**, -O-(C₁₋₆)alkyl,
 -(C₁₋₆)alkylene-**R⁷**, -SO₂-**R⁷**, -C(=O)-**R⁷**, -C(=O)OR⁷ and -C(=O)N(**R⁸**)**R⁷**;
 wherein **R⁷** and **R⁸** are as defined above;
 20 or **R⁸** and **R⁹**, together with the N to which they are attached, are linked to
 form a 4- to 7-membered heterocycle optionally further containing 1 to 3
 heteroatoms each independently selected from N, O and S, wherein each S
 heteroatom may, independently and where possible, exist in an oxidized
 state such that it is further bonded to one or two oxygen atoms to form the
 25 groups SO or SO₂;
 wherein the heterocycle is optionally substituted with 1 to 3 substituents each
 independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH,
 -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl,
 -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)
 30 alkyl and -NHC(=O)-(C₁₋₆)alkyl.

R⁶-B: In yet another alternative embodiment, **R⁶** is (C₃₋₇)cycloalkyl, aryl or **Het**, being
 optionally substituted with 1 to 3 substituents each independently selected
 from halo, (C₁₋₆)alkyl and (C₁₋₆)haloalkyl.

R⁶-C: In still another embodiment, **R⁶** is (C₃₋₇)cycloalkyl, phenyl or **Het**, optionally

substituted with 1 to 3 substituents each independently selected from halo, (C₁₋₆)alkyl and (C₁₋₆)haloalkyl;

wherein the **Het** is selected from:



R⁶-D: In another alternative embodiment, **R⁶** is (C₅₋₆)cycloalkyl, phenyl or **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl; wherein

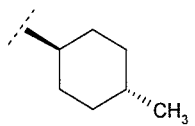
10 **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 nitrogen heteroatoms.

R⁶-E: In still another embodiment, **R⁶** is phenyl, cyclohexyl or pyridine optionally substituted with 1 to 3 substituents each independently selected from halo, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl.

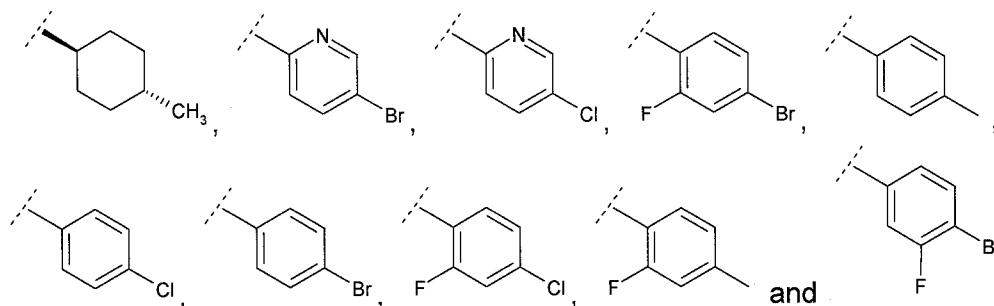
15 **R⁶-F:** In still another embodiment, **R⁶** is phenyl, optionally substituted with 1 to 3 substituents each independently selected from halo and (C₁₋₄)alkyl.

R⁶-G: In still another embodiment, **R⁶** is , optionally substituted with 1 to 3 substituents each independently selected from halo.

R⁶-H: In still another embodiment, **R⁶** is



20 **R⁶-I:** In still another embodiment, **R⁶** is selected from:



- Any and each individual definition of R^6 as set out herein may be combined with any
 5 and each individual definition of X , R^2 , R^{20} , R^3 , R^{3a} , R^{3b} and R^5 as set out herein.

Examples of preferred subgeneric embodiments of the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth above:

10

Embodiment	X	R^2	R^{20}	R^3	R^{3a}	R^{3b}	R^5	R^6
E-1	X-A	R^2 -A	R^{20} -D	R^3 -F	R^{3a} -D	R^{3b} -H	R^5 -A	R^6 -I
E-2	X-A	R^2 -A	R^{20} -D	R^3 -F	R^{3a} -D	R^{3b} -H	R^5 -A	R^6 -A
E-3	X-A	R^2 -A	R^{20} -I	R^3 -A	R^{3a} -F	R^{3b} -A	R^5 -A	R^6 -F
E-4	X-A	R^2 -A	R^{20} -B	R^3 -E	R^{3a} -H	R^{3b} -C	R^5 -B	R^6 -G
E-5	X-A	R^2 -A	R^{20} -H	R^3 -H	R^{3a} -H	R^{3b} -H	R^5 -C	R^6 -I
E-6	X-A	R^2 -A	R^{20} -A	R^3 -G	R^{3a} -H	R^{3b} -H	R^5 -D	R^6 -H
E-7	X-A	R^2 -A	R^{20} -J	R^3 -B	R^{3a} -B	R^{3b} -G	R^5 -H	R^6 -E
E-8	X-A	R^2 -B	R^{20} -H	R^3 -G	R^{3a} -H	R^{3b} -H	R^5 -H	R^6 -F
E-9	X-A	R^2 -B	R^{20} -H	R^3 -G	R^{3a} -H	R^{3b} -H	R^5 -H	R^6 -G
E-10	X-A	R^2 -B	R^{20} -H	R^3 -G	R^{3a} -H	R^{3b} -H	R^5 -H	R^6 -I
E-11	X-B	R^2 -B	R^{20} -H	R^3 -G	R^{3a} -H	R^{3b} -H	R^5 -A	R^6 -I
E-12	X-A	R^2 -C	R^{20} -F	R^3 -A	R^{3a} -D	R^{3b} -D	R^5 -A	R^6 -A
E-13	X-A	R^2 -C	R^{20} -A	R^3 -A	R^{3a} -G	R^{3b} -A	R^5 -C	R^6 -F
E-14	X-A	R^2 -C	R^{20} -B	R^3 -B	R^{3a} -A	R^{3b} -B	R^5 -D	R^6 -G
E-15	X-A	R^2 -C	R^{20} -G	R^3 -F	R^{3a} -F	R^{3b} -E	R^5 -H	R^6 -H
E-16	X-A	R^2 -C	R^{20} -E	R^3 -D	R^{3a} -E	R^{3b} -F	R^5 -H	R^6 -G
E-17	X-A	R^2 -C	R^{20} -B	R^3 -B	R^{3a} -H	R^{3b} -B	R^5 -H	R^6 -E
E-18	X-A	R^2 -D	R^{20} -D	R^3 -C	R^{3a} -F	R^{3b} -G	R^5 -E	R^6 -C
E-19	X-A	R^2 -D	R^{20} -E	R^3 -G	R^{3a} -E	R^{3b} -A	R^5 -G	R^6 -C

E-20	X-B	R ² -D	R ²⁰ -E	R ³ -G	R ^{3a} -E	R ^{3b} -G	R ⁵ -G	R ⁶ -C
E-21	X-A	R ² -D	R ²⁰ -J	R ³ -H	R ^{3a} -E	R ^{3b} -H	R ⁵ -H	R ⁶ -D
E-22	X-A	R ² -E	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-23	X-A	R ² -E	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -A
E-24	X-A	R ² -E	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -F
E-25	X-A	R ² -E	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -G
E-26	X-B	R ² -E	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -C	R ⁶ -F
E-27	X-C	R ² -E	R ²⁰ -H	R ³ -A	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -F
E-28	X-C	R ² -E	R ²⁰ -A	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -F
E-29	X-A	R ² -F	R ²⁰ -C	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁶ -G
E-30	X-A	R ² -F	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-31	X-A	R ² -F	R ²⁰ -J	R ³ -B	R ^{3a} -B	R ^{3b} -G	R ⁵ -A	R ⁶ -E
E-32	X-A	R ² -F	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-33	X-A	R ² -F	R ²⁰ -B	R ³ -E	R ^{3a} -H	R ^{3b} -C	R ⁵ -B	R ⁶ -G
E-34	X-A	R ² -F	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -C
E-35	X-A	R ² -F	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -D
E-36	X-A	R ² -G	R ²⁰ -A	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -H
E-37	X-A	R ² -G	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -C	R ⁶ -H
E-38	X-A	R ² -G	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-39	X-A	R ² -G	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -I
E-40	X-A	R ² -G	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-41	X-A	R ² -G	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-42	X-A	R ² -H	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-43	X-A	R ² -H	R ²⁰ -F	R ³ -A	R ^{3a} -E	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-44	X-A	R ² -H	R ²⁰ -B	R ³ -F	R ^{3a} -C	R ^{3b} -H	R ⁵ -C	R ⁶ -G
E-45	X-A	R ² -H	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-46	X-A	R ² -H	R ²⁰ -D	R ³ -F	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -G
E-47	X-A	R ² -H	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -E
E-48	X-A	R ² -H	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -F
E-49	X-A	R ² -I	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -G
E-50	X-A	R ² -I	R ²⁰ -B	R ³ -E	R ^{3a} -H	R ^{3b} -C	R ⁵ -B	R ⁶ -G
E-51	X-A	R ² -I	R ²⁰ -J	R ³ -B	R ^{3a} -B	R ^{3b} -G	R ⁵ -H	R ⁶ -E
E-52	X-A	R ² -J	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-53	X-A	R ² -J	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -H

E-54	X-A	R ² -J	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -B	R ⁶ -H
E-55	X-A	R ² -J	R ²⁰ -F	R ³ -A	R ^{3a} -E	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-56	X-C	R ² -J	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -C	R ⁶ -H
E-57	X-A	R ² -J	R ²⁰ -H	R ³ -G	R ^{3a} -D	R ^{3b} -H	R ⁵ -H	R ⁶ -A
E-58	X-A	R ² -J	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -I
E-59	X-B	R ² -J	R ²⁰ -H	R ³ -G	R ^{3a} -D	R ^{3b} -H	R ⁵ -H	R ⁶ -A
E-60	X-A	R ² -K	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -G
E-61	X-B	R ² -K	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-62	X-A	R ² -K	R ²⁰ -F	R ³ -A	R ^{3a} -C	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-63	X-A	R ² -K	R ²⁰ -B	R ³ -D	R ^{3a} -C	R ^{3b} -H	R ⁵ -C	R ⁶ -G
E-64	X-C	R ² -K	R ²⁰ -F	R ³ -C	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-65	X-A	R ² -K	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -F	R ⁶ -A
E-66	X-A	R ² -K	R ²⁰ -A	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -D
E-67	X-A	R ² -K	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-68	X-A	R ² -K	R ²⁰ -B	R ³ -E	R ^{3a} -H	R ^{3b} -D	R ⁵ -C	R ⁶ -A
E-69	X-A	R ² -L	R ²⁰ -A	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -G
E-70	X-A	R ² -L	R ²⁰ -D	R ³ -D	R ^{3a} -D	R ^{3b} -H	R ⁵ -C	R ⁶ -A
E-71	X-C	R ² -L	R ²⁰ -A	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -G
E-72	X-A	R ² -L	R ²⁰ -G	R ³ -G	R ^{3a} -A	R ^{3b} -E	R ⁵ -H	R ⁶ -E
E-73	X-A	R ² -L	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-74	X-A	R ² -L	R ²⁰ -G	R ³ -G	R ^{3a} -E	R ^{3b} -H	R ⁵ -H	R ⁶ -I
E-75	X-A	R ² -M	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -I
E-76	X-A	R ² -M	R ²⁰ -B	R ³ -E	R ^{3a} -H	R ^{3b} -C	R ⁵ -B	R ⁶ -G
E-77	X-A	R ² -M	R ²⁰ -J	R ³ -D	R ^{3a} -B	R ^{3b} -G	R ⁵ -H	R ⁶ -E
E-78	X-A	R ² -M	R ²⁰ -A	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -H
E-79	X-A	R ² -M	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -I
E-80	X-A	R ² -M	R ²⁰ -J	R ³ -A	R ^{3a} -F	R ^{3b} -A	R ⁵ -F	R ⁶ -F
E-81	X-B	R ² -M	R ²⁰ -I	R ³ -A	R ^{3a} -F	R ^{3b} -A	R ⁵ -F	R ⁶ -F
E-82	X-C	R ² -M	R ²⁰ -I	R ³ -A	R ^{3a} -F	R ^{3b} -A	R ⁵ -F	R ⁶ -F
E-83	X-A	R ² -N	R ²⁰ -D	R ³ -F	R ^{3a} -D	R ^{3b} -H	R ⁵ -A	R ⁶ -A
E-84	X-A	R ² -N	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-85	X-A	R ² -N	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -F
E-86	X-A	R ² -N	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-87	X-A	R ² -N	R ²⁰ -G	R ³ -G	R ^{3a} -A	R ^{3b} -C	R ⁵ -H	R ⁶ -A

E-88	X-A	R ² -N	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -B
E-89	X-A	R ² -N	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-90	X-A	R ² -O	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-91	X-A	R ² -O	R ²⁰ -F	R ³ -A	R ^{3a} -E	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-92	X-A	R ² -O	R ²⁰ -B	R ³ -F	R ^{3a} -C	R ^{3b} -H	R ⁵ -C	R ⁶ -G
E-93	X-A	R ² -O	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -F
E-94	X-A	R ² -O	R ²⁰ -D	R ³ -D	R ^{3a} -D	R ^{3b} -H	R ⁵ -C	R ⁶ -A
E-95	X-A	R ² -O	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-96	X-A	R ² -O	R ²⁰ -G	R ³ -G	R ^{3a} -A	R ^{3b} -C	R ⁵ -H	R ⁶ -E
E-97	X-A	R ² -O	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-98	X-A	R ² -O	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-99	X-A	R ² -O	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-100	X-A	R ² -O	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-101	X-A	R ² -O	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -H
E-102	X-A	R ² -O	R ²⁰ -J	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -C	R ⁶ -H
E-103	X-A	R ² -O	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -F
E-104	X-A	R ² -O	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -G
E-105	X-A	R ² -O	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-106	X-A	R ² -O	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -F
E-107	X-A	R ² -O	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -G
E-108	X-A	R ² -O	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-109	X-A	R ² -O	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -F
E-110	X-A	R ² -O	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -G
E-111	X-A	R ² -O	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -I
E-112	X-A	R ² -O	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -A	R ⁶ -H
E-113	X-A	R ² -P	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-114	X-A	R ² -P	R ²⁰ -F	R ³ -A	R ^{3a} -E	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-115	X-A	R ² -P	R ²⁰ -B	R ³ -F	R ^{3a} -C	R ^{3b} -H	R ⁵ -C	R ⁶ -G
E-116	X-A	R ² -P	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -F
E-117	X-A	R ² -P	R ²⁰ -D	R ³ -D	R ^{3a} -D	R ^{3b} -H	R ⁵ -C	R ⁶ -A
E-118	X-B	R ² -P	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -F
E-119	X-B	R ² -P	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -E
E-120	X-A	R ² -P	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-121	X-A	R ² -P	R ²⁰ -G	R ³ -G	R ^{3a} -A	R ^{3b} -C	R ⁵ -H	R ⁶ -E

E-122	X-A	R ² -P	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -C	R ⁶ -H
E-123	X-A	R ² -P	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -H
E-124	X-A	R ² -P	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -H
E-125	X-A	R ² -P	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-126	X-A	R ² -P	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -F
E-127	X-A	R ² -P	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -G
E-128	X-A	R ² -P	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -I
E-129	X-A	R ² -P	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -H
E-130	X-A	R ² -Q	R ²⁰ -A	R ³ -E	R ^{3a} -A	R ^{3b} -D	R ⁵ -A	R ⁶ -E
E-131	X-A	R ² -Q	R ²⁰ -F	R ³ -A	R ^{3a} -E	R ^{3b} -B	R ⁵ -B	R ⁶ -F
E-132	X-A	R ² -Q	R ²⁰ -B	R ³ -F	R ^{3a} -C	R ^{3b} -H	R ⁵ -C	R ⁶ -G
E-133	X-A	R ² -Q	R ²⁰ -C	R ³ -C	R ^{3a} -H	R ^{3b} -F	R ⁵ -C	R ⁶ -F
E-134	X-A	R ² -Q	R ²⁰ -D	R ³ -D	R ^{3a} -D	R ^{3b} -H	R ⁵ -C	R ⁶ -A
E-135	X-A	R ² -Q	R ²⁰ -F	R ³ -B	R ^{3a} -G	R ^{3b} -F	R ⁵ -D	R ⁶ -A
E-136	X-A	R ² -Q	R ²⁰ -H	R ³ -B	R ^{3a} -B	R ^{3b} -B	R ⁵ -E	R ⁶ -I
E-137	X-A	R ² -Q	R ²⁰ -G	R ³ -G	R ^{3a} -A	R ^{3b} -C	R ⁵ -H	R ⁶ -E
E-138	X-A	R ² -Q	R ²⁰ -H	R ³ -A	R ^{3a} -A	R ^{3b} -C	R ⁵ -H	R ⁶ -G
E-139	X-A	R ² -Q	R ²⁰ -I	R ³ -D	R ^{3a} -D	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-140	X-A	R ² -Q	R ²⁰ -I	R ³ -E	R ^{3a} -E	R ^{3b} -F	R ⁵ -H	R ⁶ -K
E-141	X-A	R ² -Q	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -H
E-142	X-A	R ² -Q	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -H
E-143	X-A	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -H
E-144	X-A	R ² -Q	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -F	R ⁶ -H
E-145	X-A	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -H
E-146	X-A	R ² -Q	R ²⁰ -J	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -H
E-147	X-A	R ² -Q	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -F
E-148	X-A	R ² -Q	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -G
E-149	X-A	R ² -Q	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -E	R ⁶ -I
E-150	X-A	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -F
E-151	X-A	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -G
E-152	X-A	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -D	R ⁶ -I
E-153	X-A	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -F
E-154	X-A	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -G
E-155	X-A	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -I

E-156	X-B	R ² -Q	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-157	X-B	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-158	X-B	R ² -Q	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-159	X-B	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -H	R ⁶ -H
E-160	X-C	R ² -Q	R ²⁰ -H	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H
E-161	X-C	R ² -Q	R ²⁰ -I	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H
E-162	X-C	R ² -Q	R ²⁰ -I	R ³ -H	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H
E-163	X-C	R ² -Q	R ²⁰ -J	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H
E-164	X-B	R ² -Q	R ²⁰ -A	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H
E-165	X-B	R ² -Q	R ²⁰ -H	R ³ -G	R ^{3a} -H	R ^{3b} -H	R ⁵ -G	R ⁶ -H

Examples of most preferred compounds according to this invention are each single compound listed in the following Tables 1 and 4.

- 5 In general, all tautomeric and isomeric forms and mixtures thereof, for example, individual geometric isomers, stereoisomers, atropisomers, enantiomers, diastereomers, racemates, racemic or non-racemic mixtures of stereoisomers, mixtures of diastereomers, or mixtures of any of the foregoing forms of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure. Compounds of the
10 invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms.

It is well-known in the art that the biological and pharmacological activity of a
15 compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one
20 enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention from this disclosure and the knowledge in the art.

Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include, for example, chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000, herein incorporated by reference. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, for example, GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, for example, CD, ORD, X-ray crystallography, or NMR.

The compounds according to the present invention are inhibitors of the hepatitis C virus NS5B RNA-dependent RNA polymerase and thus may be used to inhibit replication of hepatitis C viral RNA.

A compound according to the present invention may also be used as a laboratory reagent or a research reagent. For example, a compound of the present invention may be used as positive control to validate assays, including but not limited to surrogate cell-based assays and *in vitro* or *in vivo* viral replication assays.

Compounds according to the present invention may also be used as probes to study the hepatitis C virus NS5B polymerase, including but not limited to the mechanism of action of the polymerase, conformational changes undergone by the polymerase under various conditions and interactions with entities which bind to or otherwise interact with the polymerase.

Compounds of the invention used as probes may be labelled with a label which allows recognition either directly or indirectly of the compound such that it can be

detected, measured and quantified. Labels contemplated for use with the compounds of the invention include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes, affinity tags and photoreactive groups.

5

Compounds of the invention used as probes may also be labelled with an affinity tag whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Affinity tags include but are not limited to biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety
10 or a defined epitope recognizable by a specific antibody.

Furthermore, compounds of the invention used as probes may be labelled with a photoreactive group which is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Photoreactive groups include but
15 are not limited to photoaffinity labels such as benzophenone and azide groups.

Furthermore, a compound according to the present invention may be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with
20 such materials (e.g. blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection apparatuses and materials).

Pharmaceutical composition

Compounds of the present invention may be administered to a mammal in need of
25 treatment for hepatitis C viral infection as a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the invention or a pharmaceutically acceptable salt or ester thereof; and one or more conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The specific formulation of the composition is determined by the solubility and chemical nature of
30 the compound, the chosen route of administration and standard pharmaceutical practice. The pharmaceutical composition according to the present invention may be administered orally or systemically.

For oral administration, the compound, or a pharmaceutically acceptable salt or ester
35 thereof, can be formulated in any orally acceptable dosage form including but not

limited to aqueous suspensions and solutions, capsules, powders, syrups, elixirs or tablets. For systemic administration, including but not limited to administration by subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques, it is preferred to use a solution of the compound, or a pharmaceutically acceptable salt or ester thereof, in a pharmaceutically acceptable sterile aqueous vehicle.

Pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and additives as well as methods of formulating pharmaceutical compositions for various modes of administration are well-known to those of skill in the art and are described in pharmaceutical texts such as Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, 2005; and L.V. Allen, N.G. Popovich and H.C. Ansel, Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th ed., Lippincott Williams & Wilkins, 2004, herein incorporated by reference.

The dosage administered will vary depending upon known factors, including but not limited to the activity and pharmacodynamic characteristics of the specific compound employed and its mode, time and route of administration; the age, diet, gender, body weight and general health status of the recipient; the nature and extent of the symptoms; the severity and course of the infection; the kind of concurrent treatment; the frequency of treatment; the effect desired; and the judgment of the treating physician. In general, the compound is most desirably administered at a dosage level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

A daily dosage of active ingredient can be expected to be about 0.01 to about 200 milligrams per kilogram of body weight, with the preferred dose being about 0.1 to about 50 mg/kg. Typically, the pharmaceutical composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about

20% to about 80% active compound.

Combination therapy

Combination therapy is contemplated wherein a compound according to the
5 invention, or a pharmaceutically acceptable salt or ester thereof, is co-administered
with at least one additional antiviral agent. The additional agents may be combined
with compounds of this invention to create a single dosage form. Alternatively these
additional agents may be separately administered, concurrently or sequentially, as
part of a multiple dosage form.

10

When the pharmaceutical composition of this invention comprises a combination of
a compound according to the invention, or a pharmaceutically acceptable salt or
ester thereof, and one or more additional antiviral agent, both the compound and the
additional agent should be present at dosage levels of between about 10 to 100%,
15 and more preferably between about 10 and 80% of the dosage normally
administered in a monotherapy regimen. In the case of a synergistic interaction
between the compound of the invention and the additional antiviral agent or agents,
the dosage of any or all of the active agents in the combination may be reduced
compared to the dosage normally administered in a monotherapy regimen.

20

Antiviral agents contemplated for use in such combination therapy include agents
(compounds or biologicals) that are effective to inhibit the formation and/or
replication of a virus in a mammal, including but not limited to agents that interfere
with either host or viral mechanisms necessary for the formation and/or replication of
25 a virus in a mammal. Such agents can be selected from another anti-HCV agent; an
HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

Other anti-HCV agents include those agents that are effective for diminishing or
preventing the progression of hepatitis C related symptoms or disease. Such agents
30 include but are not limited to immunomodulatory agents, inhibitors of HCV NS3
protease, other inhibitors of HCV polymerase, inhibitors of another target in the HCV
life cycle and other anti-HCV agents, including but not limited to ribavirin,
amantadine, levovirin and viramidine.

35 Immunomodulatory agents include those agents (compounds or biologicals) that are

effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, but are not limited to, inosine monophosphate dehydrogenase inhibitors such as VX-497 (merimepodib, Vertex Pharmaceuticals), class I interferons, class II interferons, consensus interferons, asialo-interferons

5 pegylated interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin. Class I interferons are a group of interferons that all bind to receptor type I, including both naturally and synthetically produced class I interferons, while class II

10 interferons all bind to receptor type II. Examples of class I interferons include, but are not limited to, α -, β -, δ -, ω -, and τ -interferons, while examples of class II interferons include, but are not limited to, γ -interferons. In one preferred aspect, the other anti-HCV agent is an interferon. Preferably, the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A and lymphoblastoid interferon. In one preferred aspect, the

15 composition comprises a compound of the invention, an interferon and ribavirin.

Inhibitors of HCV NS3 protease include agents (compounds or biologicals) that are effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, for example, those compounds described in WO 99/07733,

20 WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/030670, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501, WO 2005/070955, WO 2006/000085, WO 2006/007700, WO 2006/007708, WO 2007/009227 (all by Boehringer Ingelheim), WO 02/060926, WO

25 03/053349, WO 03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 (all by BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune), WO 01/77113, WO 01/81325, WO 02/08187, WO 02/08198, WO 02/08244, WO 02/08256, WO 02/48172, WO

30 03/062228, WO 03/062265, WO 2005/021584, WO 2005/030796, WO 2005/058821, WO 2005/051980, WO 2005/085197, WO 2005/085242, WO 2005/085275, WO 2005/087721, WO 2005/087725, WO 2005/087730, WO 2005/087731, WO 2005/107745 and WO 2005/113581 (all by Schering), WO 2006/119061, WO 2007/016441, WO 2007/015855, WO 2007/015787 (all by

35 Merck), WO 2006/043145 (Pfizer), all of which are herein incorporated by reference;

and the candidates VX-950, SCH-503034, ITMN-191, TMC 435350, and MK7009.

- Inhibitors of HCV polymerase include agents (compounds or biologicals) that are effective to inhibit the function of an HCV polymerase. Such inhibitors include, but are not limited to, non-nucleoside and nucleoside inhibitors of NS4A, NS5A, NS5B polymerase. Examples of inhibitors of HCV polymerase include but are not limited to those compounds described in: WO 02/04425, WO 03/007945, WO 03/010140, WO 03/010141, WO 2004/064925, WO 2004/065367, WO 2005/080388, WO 2006/007693, WO 2007/019674, WO 2007/087717 (all by Boehringer Ingelheim), WO 01/47883 (Japan Tobacco), WO 03/000254 (Japan Tobacco), WO 2007/033032, WO 2007/033175, WO 2006/020082, US 2005/0119318, WO 2005/034850, WO 03/026587, WO 2007/092000, WO 2007/143521, WO 2007/136982, WO 2007/140254, WO 2007/140200, WO 2007/092888 (all by BMS), WO 2007/095269, WO 2007/054741, WO 03/062211, WO 99/64442, WO 00/06529, WO 2004/110442, WO 2005/034941, WO 2006/119975, WO 2006/046030, WO 2006/046039, WO 2005/023819, WO 02/06246, WO 2007/065883, WO 2007/129119, WO 2007/029029, WO 2006/029912, WO 2006/027628, WO 2007/028789, WO 2006/008556, WO 2004/087714 (all by IRBM), WO 2005/012288 (Genelabs), WO 2005/014543 (Japan Tobacco), WO 2005/049622 (Japan Tobacco), and WO 2005/121132 (Shionogi), WO 2005/080399 (Japan Tobacco), WO 2006/052013 (Japan Tobacco), WO 2006/119646 (Virochem Pharma), WO 2007/039146 (SmithKline Beecham), WO 2005/021568 (Biota), WO 2006/094347 (Biota), WO 2006/093801, WO 2005/019191, WO 2004/041818, US 2004/0167123, US 2005/0107364 (all by Abbott Laboratories), WO 2007/034127 (Arrow Therapeutics Limited) (all of which are herein incorporated by reference) and the candidates HCV 796 (ViroPharma/Wyeth), R-1626, R-1656 and R-7128 (Roche), NM 283 (Idenix/Novartis), VCH-759 (Virochem), GS9190 (Gilead), MK-608 (Merck) and PF868554 (Pfizer).
- The term "inhibitor of another target in the HCV life cycle" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HCV in a mammal other than by inhibiting the function HCV polymerase. This includes agents that interfere with either host or HCV viral targets necessary for the HCV life cycle or agents which specifically inhibit in HCV cell culture assays through an undefined or incompletely defined mechanism. Inhibitors

of another target in the HCV life cycle include, for example, agents that inhibit viral targets such as Core, E1, E2, p7, NS2/3 protease, NS3 helicase, internal ribosome entry site (IRES), HCV entry and HCV assembly or host targets such as cyclophilin B, phosphatidylinositol 4-kinase III α , CD81, SR-B1, Claudin 1, VAP-A, VAP-B.

- 5 Specific examples of inhibitors of another target in the HCV life cycle include ISIS-14803 (ISIS Pharmaceuticals), GS9190 (Gilead), GS9132 (Gilead), A-831 (AstraZeneca), NM-811 (Novartis), and DEBIO-025 (Debio Pharma).

10 It can occur that a patient may be co-infected with hepatitis C virus and one or more other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated is combination therapy to treat such co-infections by co-administering a compound according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

15

HIV inhibitors include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HIV. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HIV in a mammal. HIV inhibitors include, but are not limited to:

- 20 • NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors) including but not limited to zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), emtricitabine, abacavir succinate, elvucitabine, adefovir dipivoxil, lobucavir (BMS-180194) lodenosine (FddA) and tenofovir including tenofovir disoproxil and tenofovir disoproxil fumarate salt, COMBIVIR™ (contains 25 3TC and AZT), TRIZIVIR™ (contains abacavir, 3TC and AZT), TRUVADA™ (contains tenofovir and emtricitabine), EPZICOM™ (contains abacavir and 3TC);
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) including but not limited to nevirapine, delaviradine, efavirenz, etravirine and rilpivirine;
- protease inhibitors including but not limited to ritonavir, tipranavir, saquinavir, 30 nelfinavir, indinavir, amprenavir, fosamprenavir, atazanavir, lopinavir, darunavir, lasinavir, brecanavir, VX-385 and TMC-114;
- entry inhibitors including but not limited to
- CCR5 antagonists (including but not limited to maraviroc, vicriviroc, INCB9471 and TAK-652),
- 35 • CXCR4 antagonists (including but not limited to AMD-11070),

- fusion inhibitors (including but not limited to enfuvirtide (T-20), TR1-1144 and TR1-999) and
- others (including but not limited to BMS-488043);
- integrase inhibitors (including but not limited to raltegravir (MK-0518), BMS-707035 and elvitegravir (GS 9137));
- TAT inhibitors;
- maturation inhibitors (including but not limited to berivimat (PA-457));
- immunomodulating agents (including but not limited to levamisole); and
- other antiviral agents including hydroxyurea, ribavirin, IL-2, IL-12 and pensafuside.

HAV inhibitors include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HAV. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HAV in a mammal. HAV inhibitors include but are not limited to Hepatitis A vaccines.

HBV inhibitors include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HBV in a mammal. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HBV in a mammal. HBV inhibitors include, but are not limited to, agents that inhibit the HBV viral DNA polymerase and HBV vaccines.

Therefore, according to one embodiment, the pharmaceutical composition of this invention additionally comprises a therapeutically effective amount of one or more antiviral agents.

A further embodiment provides the pharmaceutical composition of this invention wherein the one or more antiviral agent comprises at least one other anti-HCV agent.

According to a more specific embodiment of the pharmaceutical composition of this invention, the at least one other anti-HCV agent comprises at least one immunomodulatory agent.

According to another more specific embodiment of the pharmaceutical composition

of this invention, the at least one other anti-HCV agent comprises at least one other inhibitor of HCV polymerase.

According to yet another more specific embodiment of the pharmaceutical
5 composition of this invention, the at least one other anti-HCV agent comprises at least one inhibitor of HCV NS3 protease.

According to still another more specific embodiment of the pharmaceutical
composition of this invention, the at least one other anti-HCV agent comprises at
10 least one inhibitor of another target in the HCV life cycle.

EXAMPLES

Other features of the present invention will become apparent from the following non-limiting examples which illustrate, by way of example, the principles of the invention.

15 As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting
20 groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981), and more recent editions thereof, herein incorporated by reference. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume
25 relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO₂) according to the procedure of W.C. Still *et al.*, J. Org. Chem., (1978), 43, 2923. Mass spectral analyses are recorded using electrospray mass spectrometry. Purification on a combiflash is performed using an Isco Combiflash (column cartridge SiO₂). Preparative HPLC is carried out under standard conditions using a
30 SunFire™ Prep C18 OBD 5µM reverse phase column, 19 x 50 mm and a linear gradient (20 to 98%) employing 0.1%TFA/acetonitrile and 0.1%TFA/water as solvents. Compounds are isolated as TFA salts when applicable. Analytical HPLC is carried out under standard conditions using a Combiscreen™ ODS-AQ C18 reverse phase column, YMC, 50 x 4.6 mm i.d., 5 µM, 120 Å at 220 nM, elution with a
35 linear gradient as described in the following table (Solvent A is 0.06% TFA in H₂O;

solvent B is 0.06% TFA in MeCN):

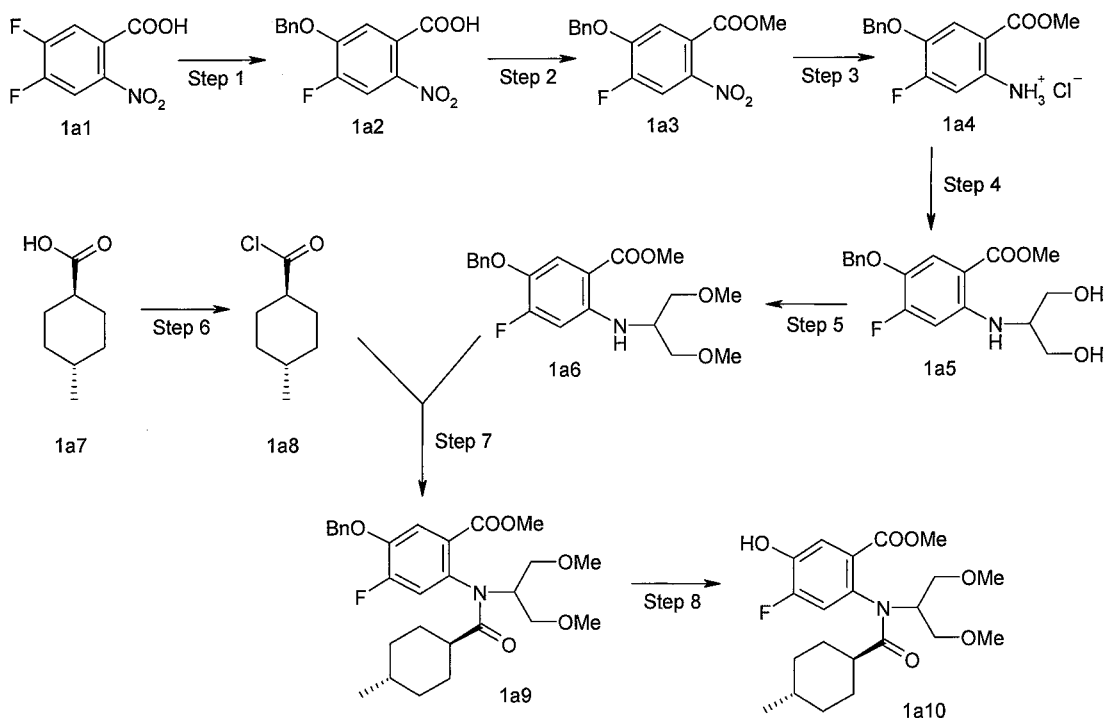
Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	3.0	95	5
0.5	3.0	95	5
6.0	3.0	50	50
10.5	3.5	0	100

Abbreviations or symbols used herein include:

- 5 Ac: acetyl;
 AcOH: acetic acid;
 BINAP: (2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene;
 Bn: benzyl (phenylmethyl);
 BOC or Boc: *tert*-butoxycarbonyl;
- 10 Bu: butyl;
n-BuLi: *n*-butyllithium;
n-BuOAc: *n*-butylacetate;
m-CPBA: *meta*-chloroperbenzoic acid;
 DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;
- 15 DCE: dichloroethane;
 DCM: dichloromethane;
 DEAD: diethyl azodicarboxylate;
 DIAD: diisopropyl azodicarboxylate;
 DIPEA: diisopropylethylamine;
- 20 DMAP: 4-dimethylaminopyridine;
 DMF: *N,N*-dimethylformamide;
 DMSO: dimethylsulfoxide;
 EC₅₀: 50% effective concentration;
 Et: ethyl;
- 25 Et₃N: triethylamine;
 Et₂O: diethyl ether;
 EtOAc: ethyl acetate;
 EtOH: ethanol;
 HATU: 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium
- 30 hexafluorophosphate Methanaminium;

- Hex: hexane;
HPLC: high performance liquid chromatography;
IC₅₀: 50% inhibitory concentration;
*i*Pr or *i*-Pr: 1-methylethyl (*iso*-propyl);
5 LC-MS: liquid chromatography-mass spectrometry;
LDA: lithium diisopropylamide;
Me: methyl;
MeCN: acetonitrile;
MeI: iodomethane;
10 MeOH: methanol;
MS: mass spectrometry (ES: electrospray);
NaHB(OAc)₃: sodium triacetoxyborohydride;
NaHMDS: sodium hexamethyldisilazane;
NIS: *N*-iodosuccinamide;
15 NMO: *N*-methylmorpholine-*N*-oxide;
NMP: *N*-methylpyrrolidone;
NMR: nuclear magnetic resonance spectroscopy;
Ph: phenyl;
Pr: *n*-propyl;
20 Psi: pounds per square inch;
Rpm: rotations per minute;
RT: room temperature (approximately 18°C to 25°C);
tert-butyl or *t*-butyl: 1,1-dimethylethyl;
tert-BuOH or *t*-BuOH: *tert*-butanol
25 TBABr: tetrabutylammonium bromide;
TBAF: tetrabutylammonium fluoride;
TBDPS: *tert*-butyldiphenylsilyloxy;
TFA: trifluoroacetic acid;
THF: tetrahydrofuran;
30 TLC: thin layer chromatography.

EXAMPLE 1A**Preparation of intermediate 1a10**

**Step 1:**

1a1 (73 g, 35 mmol) is diluted in anhydrous THF (2 L) under Ar. Benzyl alcohol (80.8 mL, 800 mmol) is added and the mixture is chilled to 0°C. Sodium bis(trimethylsilyl)amide (1.0 M in THF, 800 mL, 800 mmol) is added dropwise. After stirring for about 1 h, the mixture is partitioned between saturated aqueous NH₄Cl and EtOAc. The organic phase is collected and dried over Na₂SO₄. The mixture is filtered and concentrated under reduced pressure. The resulting solid **1a2** is washed with cold EtOAc and dried.

10 **Step 2:**

Carboxylic acid **1a2** (112.8 g, 384 mmol) is diluted in anhydrous DMF (2 L). Potassium carbonate (108.1 g, 775 mmol) is added and the mixture is chilled to 0°C. Iodomethane (110 g, 775 mmol) is added dropwise and after about 2 h, the reaction is quenched by the addition of saturated aqueous NH₄Cl. The aqueous solution is extracted with EtOAc (2x). The combined organic extracts are washed with water and brine before being dried with MgSO₄. Removal of solvent results in methyl ester **1a3**.

Step3:20 **Step 3a:**

The nitro intermediate **1a3** (63.8 g, 212 mmol) is diluted in THF (1 L). Aqueous HCl (1 M, 500 mL, 500 mmol) is added followed by tin powder (55 g, 46 mmol). The mixture is stirred for about 2 h at RT. The reaction mixture is diluted with EtOAc and the pH of the mixture is adjusted to approximately 7 by the addition of 1 N NaOH.

- 5 The organic phase is separated, washed with water and brine, dried over Na₂SO₄ and solvent is removed to afford aniline.

Step 3b:

- 10 The aniline (97.1 g, 377 mmol) is combined with anhydrous Et₂O (1 L) and is then treated by the slow addition of HCl (2 M in ether, 2 L). The resulting hydrochloride salt **1a4** is collected by filtration and washed with excess ether.

Step 4:

- 15 The aniline hydrochloride salt **1a4** (1.04 g, 3.33 mmol) and 1,3-dihydroxyacetone (1.84 g, 20.4 mmol) are combined in dry MeOH (40 mL). After stirring for about 15 min, whereupon the homogeneous solution turns vivid red, a solution of sodium cyanoborohydride (1.05 g, 16.7 mmol) pre-dissolved in MeOH (5 mL) is slowly added over about 5 min. The reaction is neutralized by slowly adding a saturated aqueous solution of NaHCO₃ (3 mL), then the mixture is concentrated to dryness. The
20 remaining solid is purified by flash chromatography (2% to 5% MeOH gradient in DCM) to afford diol **1a5**.

Step 5:

- 25 The diol **1a5** (1.89 g, 5.40 mmol) and methyl iodide (1.0 mL, 16.2 mmol) are dissolved in dry DMF (20 mL) and cooled to 0°C. A suspension of sodium hydride (60% w/w, 453 mg, 11.3 mmol) in DMF (5 mL) is slowly added over about 15 min and the reaction is stirred at RT. The reaction is neutralized at 0°C by adding a saturated aqueous solution of NH₄Cl (10 mL). The mixture is diluted with EtOAc and the layers are separated. The organic layer is washed with water (2x) and brine (1x).
30 The combined organic phases are dried over MgSO₄, filtered and concentrated under reduced pressure. Following purification by flash chromatography (10% to 25% EtOAc gradient in hexane), dimethoxy **1a6** is isolated.

Step 6:

- 35 To a mixture of compound **1a7** (43.4 g, 305 mmol) in anhydrous DCM (400 mL)

under an Ar atmosphere is added oxalyl chloride (53.2 mL, 610 mmol) in DCM (305 mL) over about 1 h. The mixture is stirred for about 1 h at RT and anhydrous DMF (1 mL) is added dropwise. The mixture is stirred overnight at RT and concentrated under reduced pressure. The residue is diluted with pentane and filtered. The filtrate is concentrated under reduced pressure, diluted with pentane and filtered, then concentrated under reduced pressure to provide acid chloride **1a8**.

Step 7:

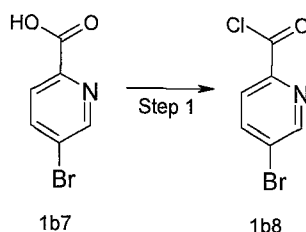
The aniline **1a6** (1.25 g, 3.31 mmol) is combined with anhydrous pyridine (3 mL) and a catalytic amount of DMAP (121 mg, 0.99 mmol). A pre-mixed solution of acid chloride **1a8** (1.35 g, 8.40 mmol) in DCE (4.2 mL) is then added. The mixture is heated to 115°C overnight, and then allowed to cool before being neutralized with a saturated aqueous solution of NaHCO₃. The mixture is extracted with EtOAc (3x). The combined organic phases are washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue is purified by combiflash (EtOAc gradient in Hex) to yield amide **1a9**.

Step 8:

Benzyl ether **1a9** (1.28 g, 2.55 mmol) is dissolved in MeOH (10 mL) and EtOAc (20 mL) and the mixture is purged with N₂ (2x). 10% Pd/C (20 mg) is added and the vessel is kept under an atmosphere of H₂ (balloon) for about 2 h. The mixture is then filtered through a pad of Celite® and rinsed with an excess MeOH. The filtrate is concentrated under reduced pressure and the residue is purified by flash chromatography (2% to 5% MeOH in DCM) to afford **1a10**.

EXAMPLE 1B

Preparation of intermediate **1b8**



Step 1:

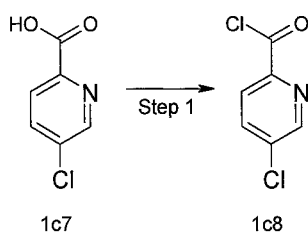
Compound **1b7** is transformed to compound **1b8** using the procedure described in

Example 1A, Step 6.

EXAMPLE 1C

Preparation of intermediate 1c8

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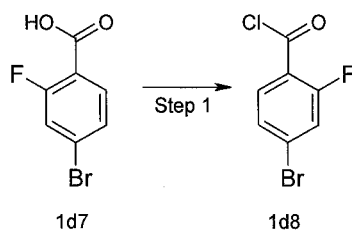


Step 1:

Compound **1c7** is transformed to compound **1c8** using the procedure described in Example 1A, Step 6.

10 EXAMPLE 1D

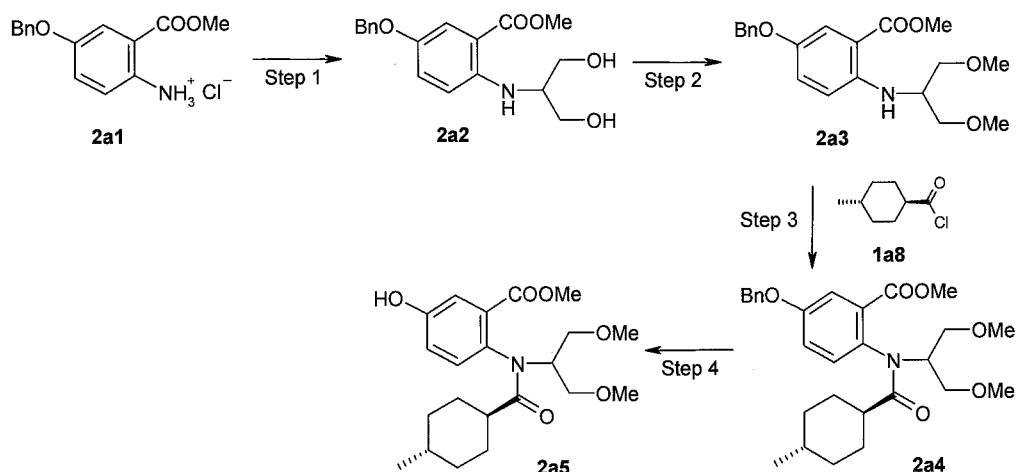
Preparation of intermediate 1d8



Step 1:

Compound **1d7** is transformed to compound **1d8** using the procedure described in Example 1A, Step 6.

15

EXAMPLE 2A**Preparation of intermediate 2a5**Step 1:

- 5 The aniline hydrochloride salt **2a1** (preparation described in WO2007/087717) is coupled with 1,3-dihydroxyacetone according to the conditions described in Step 4, Example 1A to provide diol **2a2**.

Step 2:

- 10 Compound **2a2** is transformed to dimethoxy **2a3** using the procedure of Step 5, Example 1A.

Step 3:

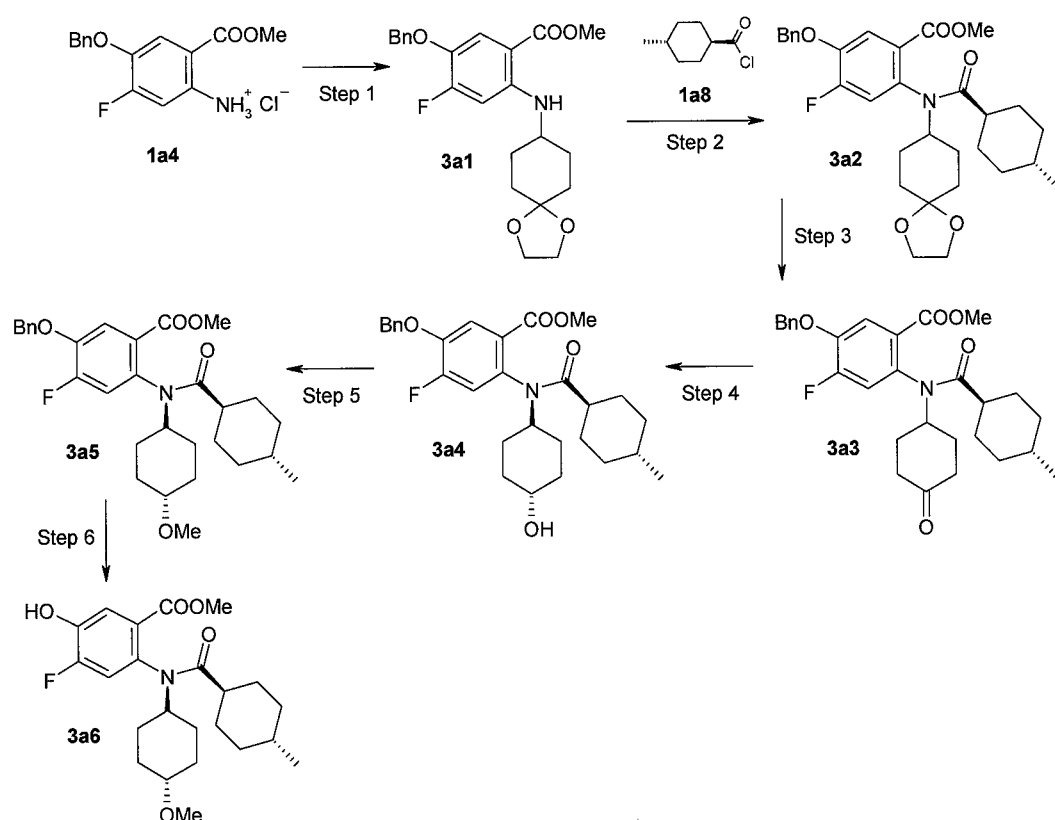
- Compound **2a3** is transformed to compound **2a4** using the procedure of Step 7, Example 1A.
- 15

Step 4:

Benzyl ether **2a4** is transformed to compound **2a5** using the procedure of Step 8, Example 1A.

20

EXAMPLE 3A**Preparation of intermediate 3a6**

**Step 1:**

- The hydrochloride aniline salt **1a4** (25.0 g, 90.7 mmol) is dissolved in anhydrous THF (60 mL) under Ar. 1,4-cyclohexanedione monoethylene ketal (14.3 g, 91.6 mmol) is added at RT followed by dibutyltin dichloride (1.38 g, 4.54 mmol). The mixture is stirred for about 15 min and then phenylsilane (23.0 mL, 99.8 mmol) is slowly added. The mixture is stirred at RT for about 2 days. Solvent is partially removed and the residue is dissolved in EtOAc and washed with saturated aqueous solution of NaHCO₃ followed by water and brine. The organic phases are dried over Na₂SO₄, filtered and the solvents are removed under reduced pressure to give an oily solid.
- This crude material is redissolved in EtOAc and an equal volume of hexanes is added followed by cooling at 0°C. As a result, a biphasic mixture with a solid is obtained. The liquid is decanted and the resulting solid is washed with hexanes. After drying, **3a1** is isolated.

Step 2:

To a solution of the ketal **3a1** (15.0 g, 36.1 mmol) in toluene (100mL) under Ar is added the acid chloride **1a8** (9.73 g, 59.1 mmol) followed by pyridine (10 mL, 123 mmol). The mixture is heated to reflux overnight. EtOAc is added and the organic layer is washed successively with water, 10% citric acid solution, saturated solution

of NaHCO₃ and brine. The mixture is dried over Na₂SO₄ and the solvent is removed under reduced pressure. Following purification by flash chromatography (10% EtOAc in hex), product **3a2** is isolated.

5 Step 3:

To a solution of the ketal **3a2** (13.8 g, 25.5 mmol) in toluene (50 mL) is added TFA (50 mL). After about 1 h, water (3 mL) is added and the mixture is stirred overnight. The solvents are evaporated and the crude residue is dissolved in EtOAc. The organics are successively washed with a 5% aqueous solution of K₂CO₃, water and
10 brine, then dried over Na₂SO₄. Solvents are removed under reduced pressure to afford **3a3** which is used without further purification.

Step 4:

To a cold solution (0 °C) of the ketone **3a3** (13.5 g, 25.5 mmol) in MeOH (200 mL) is
15 added portionwise NaBH₄ (0.40 g, 12.7 mmol). The reaction is stirred at 0°C until complete conversion, then a 1 M HCl solution is slowly added. Solvent is removed under reduced pressure and the residue is dissolved in EtOAc. The organics are successively washed with a saturated aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄. Solvents are removed under reduced pressure and the
20 crude residue is purified by flash chromatography (EtOAc in hex) to give the *trans* alcohol **3a4**.

Step 5:

The alcohol **3a4** (5.0 g, 10.1 mmol) is dissolved in DMF (50 mL) and cooled to 0°C
25 prior to adding NaH (0.81 g, 29.1mmol) followed by MeI (42 g, 301 mmol). After being stirred at 0°C for about 2 h, the reaction is quenched by the addition of a 1 M HCl solution. A large volume of EtOAc is added and the organics are successively washed with a saturated aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄. Removal of the solvent under reduced pressure gives **3a5** which is
30 used without further purification.

Step 6:

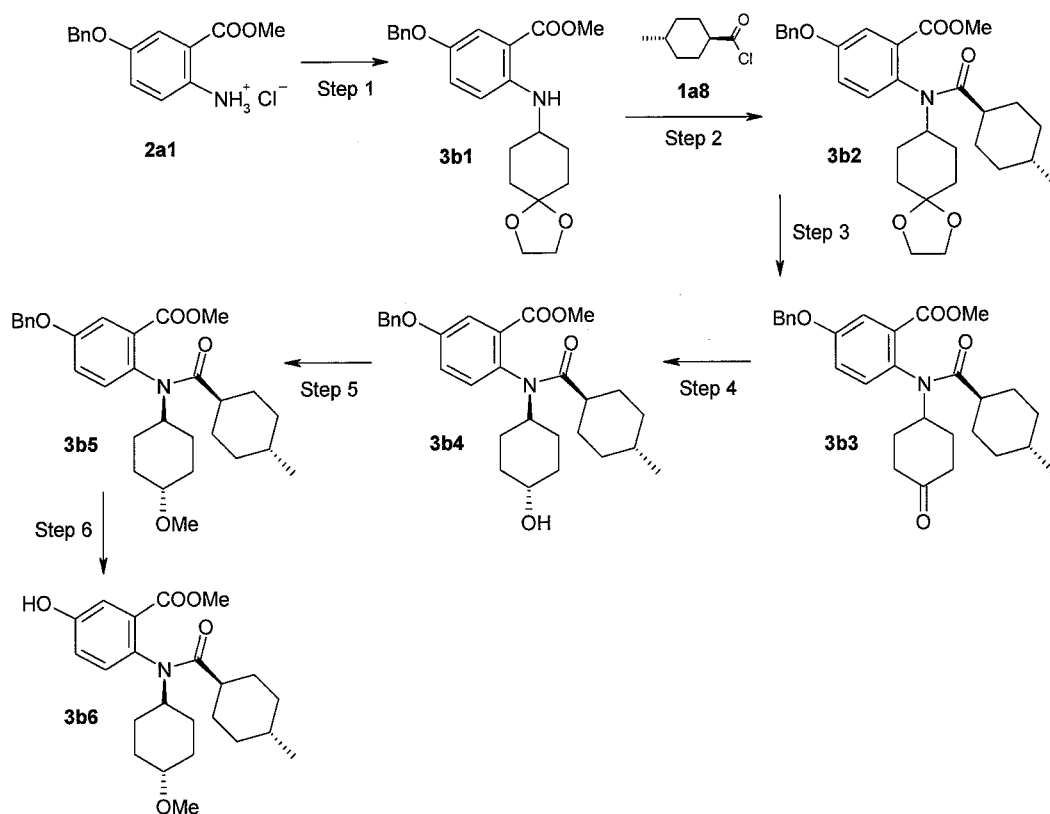
In a Parr Hydrogenator™, the ether **3a5** (5.0 g, 9.77mmol) is dissolved in MeOH (120mL) and 10% Pd/C (0.75 g) is added. The vessel is pressurized to 30 psi of H₂
35 and agitated overnight. The mixture is filtered through a pad of Celite®, then

concentrated *in vacuo* to afford phenol **3a6**.

EXAMPLE 3B

Preparation of intermediate **3b6**

5



Step 1:

The aniline hydrochloride salt **2a1** (preparation described in WO2007/087717) is coupled with 1,4-cyclohexanedione monoethylene ketal according to the conditions described in Step 1, Example 3A to produce ketal **3b1**.

Step 2:

Compound **3b1** is transformed to amide **3b2** using the procedure of Step 2, Example 3A.

15

Step 3:

Ketal **3b2** is transformed to ketone **3b3** using the procedure of Step 3, Example 3A.

Step 4:

Ketone **3b3** is transformed to alcohol **3b4** using the procedure of Step 4, Example 3A.

Step 5:

- 5 Alcohol **3b4** is transformed to compound **3b5** using the procedure of Step 5, Example 3A.

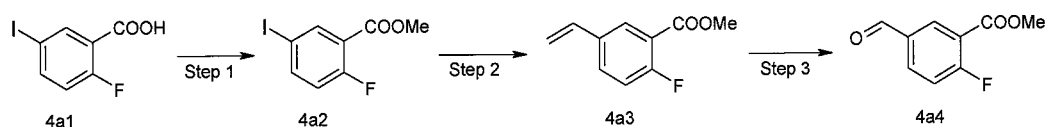
Step 6:

Ether **3b5** is transformed to phenol **3b6** using the procedure of Step 6, Example 3A.

10

EXAMPLE 4A

Preparation of intermediate 4a4



Step 1:

- 15 To a stirring mixture of **4a1** (25 g, 24 mmol) in MeCN (500 mL) and DMF (50 mL) chilled to -5 °C is added DBU (15.4 mL, 103 mmol) followed by the slow addition of MeI (8.8 mL, 141 mmol). The mixture is allowed to warm to RT and is stirred overnight. The mixture is poured into water (1 L); then extracted with EtOAc (500 mL x 3). The combined organic extracts are washed with brine, dried over Na₂SO₄,
 20 filtered and concentrated under reduced pressure. Crude ester **4a2** is utilized without further purification.

Step 2:

- To a mixture of iodoarene **4a2** (22.3 g, 79 mmol) in dioxane (200 mL) is added
 25 tributylvinyltin (20 mL, 68 mmol). The mixture is degassed with Ar before (Ph₃P)₄Pd (2.4 g, 2.1 mmol) is added. The mixture is refluxed for about 1 h then stirred at RT overnight. The mixture is concentrated under reduced pressure and the resulting residue is subjected to flash chromatography to isolate alkene **4a3**.

30 Step 3:

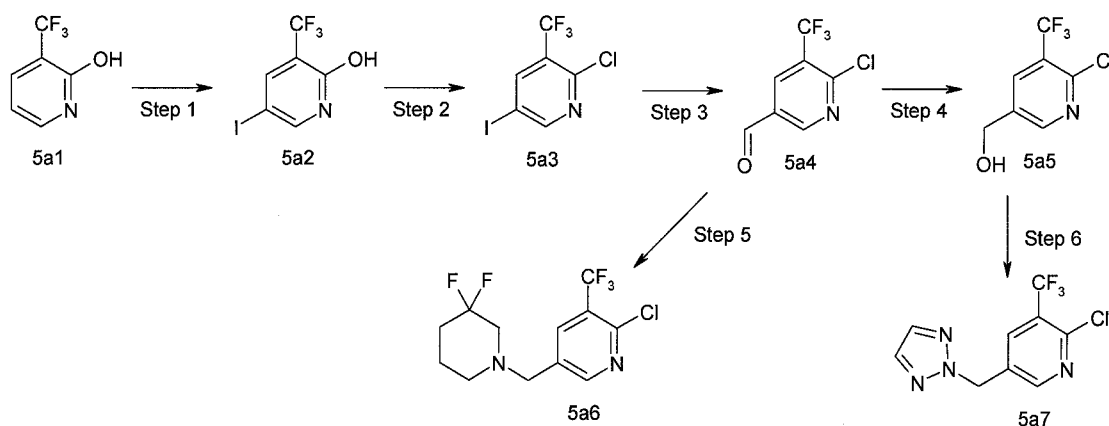
To a mixture of alkene **4a3** (9.6 g, 89 mmol) in THF (360 mL) and water (270 mL) is added OsO₄ (2.5% solution in *t*-BuOH, 5.4 mL) followed by the portionwise addition

of NaIO_4 (34 g, 160 mmol). The mixture is stirred for about 2 h at RT before being partially concentrated and diluted in EtOAc. The organic phase is washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue is subjected to flash chromatography to isolate aldehyde **4a4**.

5

EXAMPLE 5A

Preparation of intermediates **5a6** and **5a7**



Step 1:

2-Hydroxy-3-trifluoromethylpyridine (500 g, 3.06 mol) is placed in a 22 L round bottom flask under Ar. Anhydrous DMF (8 L) is added followed by potassium carbonate (430 g, 1 eq) and *N*-iodosuccinimide (700 g, 1 eq). The mixture is stirred under Ar and heated to an internal temperature of 55°C for about 2 h. The heating is removed and the suspension stirred overnight. The mixture is filtered and the solvent removed. The residue is dissolved in DCM (8 L) and water (4 L) is added. The mixture is stirred and acidified to approximately pH 3-4 with HCl. The organic phases are separated and the aqueous phase extracted with additional DCM. The organics are combined, washed with brine and dried over MgSO_4 . Cooling of the DCM and concentration affords the product **5a2** as a precipitate.

Step 2:

The phenol **5a2** (125 g, 424 mmol) is placed in a 3-neck 2 L flask. Phenylphosphonic dichloride (500 mL) is added and the mixture heated to 136°C under Ar with stirring. After consumption of starting material (about 4-5 h), the reaction is cooled to RT and carefully quenched by the slow addition of the reaction mixture to crushed ice (**caution**: very exothermic!). A white solid forms which is filtered. The solid is

dissolved in EtOAc (2 L) and aqueous NaOH is added with stirring. A NaOH solution is added until the aqueous layer is neutral. The EtOAc layer is separated, washed with water and brine and dried over anhydrous Na₂SO₄. Removal of solvent gives a white solid which is washed with cold hexane to afford chloride **5a3**.

5

Step 3:

Iodide **5a3** (10 g, 32.5 mmol) is combined with a 1:3 mixture of anhydrous THF and anhydrous toluene (100 mL) under an Ar atmosphere. The mixture is cooled to -78°C then *n*-BuLi (1.6 M in hexanes, 24 mL, 38.4 mmol) is added slowly by syringe over about 40 min. Stirring is continued for about 1 h before ethylformate (3.2 mL, 39.7 mmol) in THF (10 mL) is added over a period of about 40 min. The mixture is stirred for about 1 h before being quenched by the addition of 2 M HCl. The mixture is partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase is collected, washed with brine and dried over Na₂SO₄. The mixture is filtered and concentrated under reduced pressure. Purification is performed by flash chromatography where the silica gel is pre-treated with 3% Et₃N in hexanes then eluted with 1:1 EtOAc/Hex to isolate aldehyde **5a4**.

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15

Step 4:

A mixture of aldehyde **5a4** (19 g, 81 mmol) in MeOH (225 mL) is chilled to 0°C. Sodium borohydride (4.1 g, 109 mmol) is added portionwise and the mixture is stirred at 0°C for about 1.5 h. Another portion of NaBH₄ (1 g) is added and the mixture is stirred for about another 30 min. The reaction is quenched by the addition of NaHSO₄ (5% aqueous) then diluted in EtOAc (500 mL). The organic phase is separated then washed with water (500 mL) and brine. The organic phase is dried over Na₂SO₄, filtered then concentrated under reduced pressure. The residue is subjected to flash chromatography (1:1 EtOAc/Hex) to isolate alcohol **5a5**.

20
25

Step 5:

To the crude aldehyde **5a4** (2 g, 9.5 mmol) in 45 mL of DCE is added difluoropiperidine-HCl salt (1.6 g, 10.5 mmol) and triacetoxy sodium borohydride (2.8 g, 13.4 mmol). This reaction is stirred overnight at RT. The mixture is diluted with EtOAc (300 mL) and washed with water (100 mL) and brine (100mL). The organic phase is then dried over MgSO₄, filtered and concentrated. The residue is purified by flash chromatography (Combiflash, 15-40% EtOAc/Hex.) to afford **5a6** as an orange

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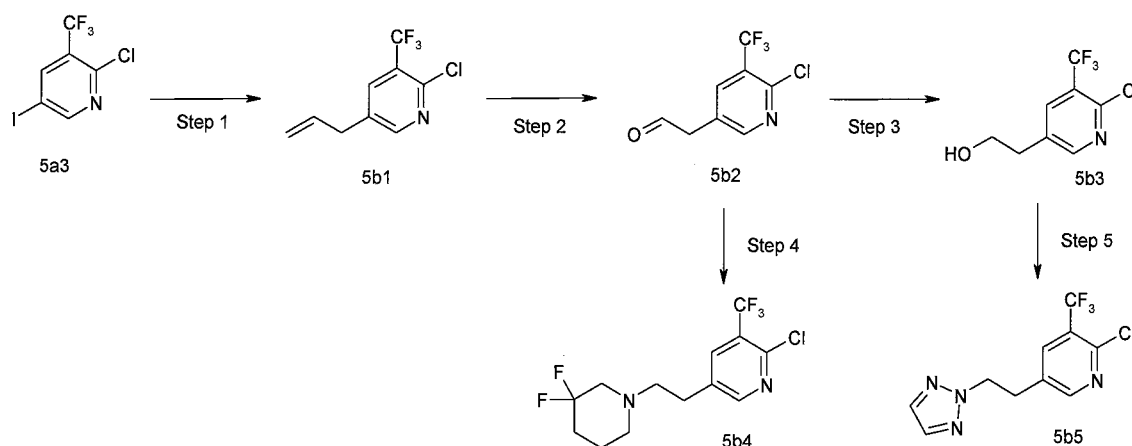
oil.

Step 6:

Alcohol **5a5** (10.5 g, 48 mmol) is combined with triazole (3.42 g, 48 mmol) and triphenylphosphine (14.3 g, 54 mmol) in anhydrous THF (500 mL). The mixture is chilled to 0°C and DIAD (10.6 mL, 54 mmol) is added dropwise. Stirring continues at 0°C for about 1 h before the mixture is allowed to warm to RT and is then stirred overnight. The mixture is diluted in EtOAc and washed with water (500 mL) and brine (500 mL) before being dried over Na₂SO₄. The solvents are removed under reduced pressure and the residue is subjected to flash chromatography (1:3 EtOAc/Hex) to afford benzylic triazole **5a7**.

EXAMPLE 5B

Preparation of intermediates **5b4** and **5b5**



Step 1:

To a solution of iodide **5a3** (300 mg, 0.98 mmol) in THF (3 mL) is added *i*-PrMgCl (0.54 mL 2.0 M soln in THF) at -40 °C. The reaction mixture is stirred for about 30 min and allyl bromide (0.13 mL, 1.5 mmol) is then added. This mixture is stirred at -40 °C for about 15 min and then stirring is continued at RT for about 30 min. The mixture is quenched with water and extracted with EtOAc (3x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. A light brown oil **5b1** is obtained which is employed without further purification in the subsequent step.

Step 2:

Alkene **5b1** is transformed to aldehyde **5b2** using the procedure described in Step 3, Example 4A.

5 Step 2:

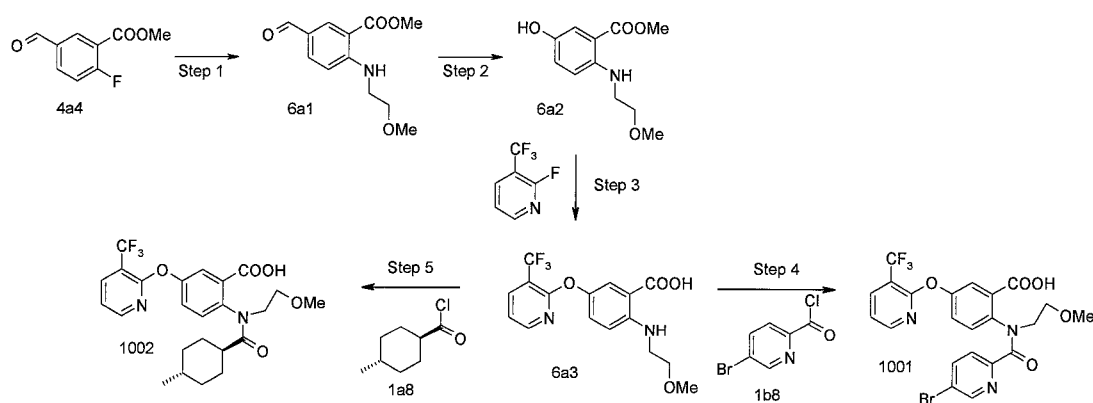
Aldehyde **5b2** is transformed to alcohol **5b3** using the procedure described in Step 4, Example 5A.

Step 4:

10 Aldehyde **5b2** is transformed to compound **5b4** using the procedure of Step 5, Example 5A.

Step 5:

15 Alcohol **5b3** is transformed to triazole **5b5** using the procedure of Step 6, Example 5A.

EXAMPLE 6A**Preparation of compounds 1001 and 1002**20 Step 1:

To an 8-mL vial are successively added K_2CO_3 (46 mg, 0.33 mmol), aldehyde **4a4** (50 mg, 0.275 mmol in 0.5 mL DMSO) and 2-methoxyethylamine (103.9 mg, 1.4 mmol). The mixture is agitated on a J-Kem® orbital shaker (270 rpm) at 70°C overnight. Water (1 mL) and concentrated HCl (0.7 mL) are added to the mixture.

25 The mixture is heated at 70°C for about 3 h, extracted with EtOAc (2 mL) and washed with H_2O (3x). After concentration, the crude aniline **6a1** is obtained and used as such in the following step.

Step 2:

To the crude aldehyde **6a1** dissolved in MeOH (1.5 mL in an 8-mL vial) at 2°C are successively added hydrogen peroxide (43 µL of a 30% aqueous solution) and concentrated H₂SO₄ (20 µL). The mixture is agitated on a J-Kem® orbital shaker (290 rpm) at 2°C for about 15 min and then a saturated aqueous solution of NaCl is added (2 mL). The mixture is extracted with EtOAc (2 mL) and the combined organic extracts are successively washed with water (1 mL) and brine (1 mL). The organic phase is dried with MgSO₄, filtered and concentrated to afford the crude phenol **6a2** which is used as such in the following step.

Step 3:

To the crude phenol **6a2** obtained above in dry DMSO (0.5 mL) are successively added K₂CO₃ (133 mg, 0.96 mmol) and 2-fluoro-3-trifluoromethylpyridine (40 µL, 0.33 mmol). The suspension is agitated overnight on a J-Kem® orbital shaker (290 rpm) at 85°C. Aqueous NaOH solution (5 N, 250 µL) is added at RT and the reaction mixture is agitated at 50°C for about 3 h. After acidification using a 1 N aqueous KHSO₄ solution, the mixture is extracted with EtOAc (3x). The combined organic extracts are successively washed with water and brine, dried over MgSO₄ and filtered. After concentration, the residue is dissolved in a mixture of DMSO and AcOH (1.5 mL) and purified by reverse phase preparative LC-MS. Conditions; column: Agilent SB-C18, 5 µM, 21.2 mm X 50 mm; gradient: 5% to 100% H₂O 0.06% TFA/MeCN 0.06% TFA; flow: 30 mL/min for 13.5 min; makeup: 25% H₂O 0.05% Ammonium formate/75% MeCN; 1 mL/min. After lyophilization the desired ether **6a3** is isolated.

Step 4:

To a mixture of aniline **6a3** (10.0 mg, 0.028 mmol) in DCE (0.3 mL) is added acid chloride **1b8** (6.31 mg, 0.039 mmol) and pyridine (9.8 µL, 0.121 mmol). The mixture is heated at 150°C for 15 min in a microwave. After concentration, the residue is dissolved in DMSO and AcOH, and purified by reverse phase preparative LC-MS. Conditions; column: Agilent SB-C18, 5 µM, 21.2 mm X 50 mm; gradient: 5% to 100% H₂O 0.06% TFA/MeCN 0.06% TFA; flow: 30 mL/min for 13.5 min; makeup: 25% H₂O 0.05% Ammonium formate/75% MeCN; 1 mL/min. After lyophilization compound

1001 is isolated.

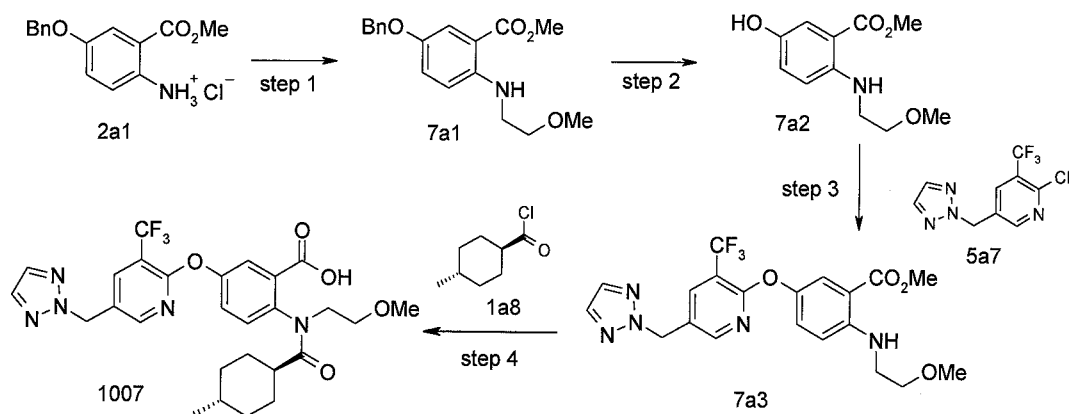
Step 5:

Amine **6a3** is transformed to compound **1002** using the procedure in Step 2,

5 Example 3a.

EXAMPLE 7A

Preparation of compound 1007



10 Step1

2-Bromoethyl methyl ether (2.22 g, 15.9 mmol) is added to aniline **2a1** (712.0 mg, 2.42 mmol) dissolved in dry DMF (8.0 mL) in a pressure tube. KI (2.0 g, 12.0 mmol) is added, followed by DIPEA (2.72 mL, 16.0 mmol) and the mixture is heated at 120°C for about 16 h. The mixture is cooled to RT, diluted with aqueous saturated NaHCO₃ (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (20% EtOAc in hexanes) to afford **7a1**.

20 Step 2

Benzyl ether **7a1** is transformed to phenol **7a2** using the procedure described in Step 8, Example 1A.

Step 3

25 Potassium carbonate (19 mg, 1.4 mmol) is added to a DMSO solution (3.0 mL) of phenol **7a2** (100 mg, 0.44 mmol) and chloropyridine **5a7** (6.6 mg, 0.44 mmol). The

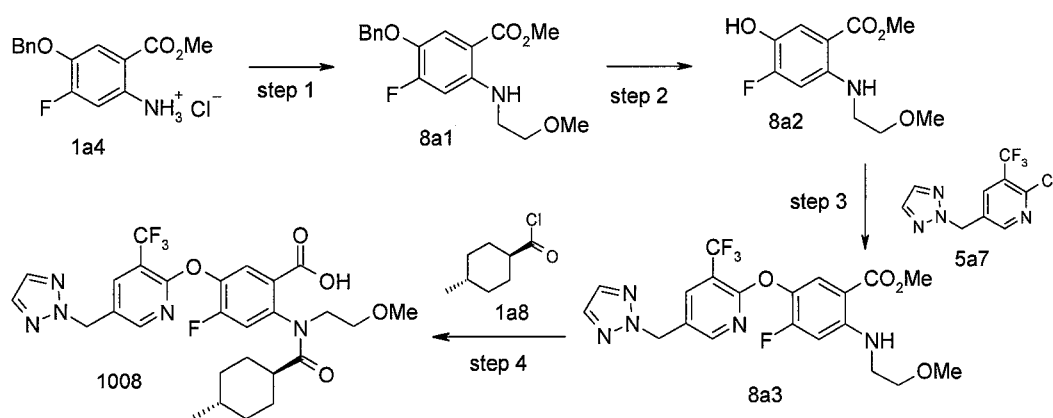
mixture is heated at 70°C for about 20 h. The solution is cooled to RT, diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (40% EtOAc in hexanes) to afford triazole **7a3** (158.0 mg, 79% yield).

Step 4

Pyridine (27 µL, 0.33 mmol) is added to a DCE solution (0.5 mL) of aniline **7a3** (50 mg, 0.11 mmol) and acid chloride **1a8** (21.4 mg, 0.113 mmol). The mixture is heated at 150°C in a microwave for 15 min. The solution is cooled to RT and concentrated under reduced pressure. The residue is dissolved in DMSO (1 mL) and then 2.5 N NaOH (0.4 mL) is added. The solution is stirred at 50°C for about 1 h; then acidified with AcOH and purified by preparative HPLC to afford **1007**.

EXAMPLE 8A

Preparation of compound 1008



Step1

Aniline **1a4** is transformed to compound **8a1** using the procedure described in Step 1, Example 7A.

Step 2

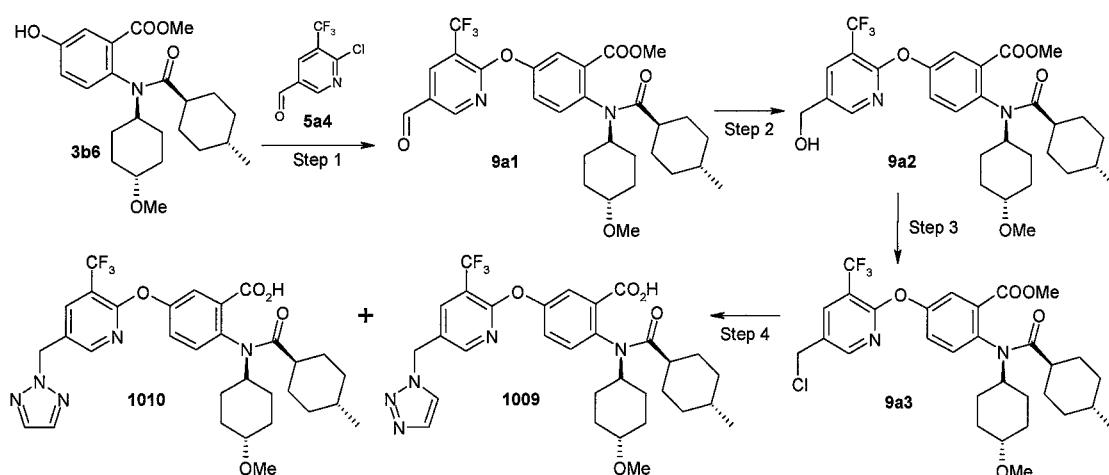
Benzyl ether **8a1** is transformed to compound **8a2** using the procedure described in Step 8, Example 1A.

Step 3

Phenol **8a2** is transformed to triazole **8a3** using the procedure described in Step 3, Example 7A.

5 Step 4

Amine **8a3** is transformed to compound **1008** using the procedure described in Step 4, Example 7A.

EXAMPLE 9A10 **Preparation of compounds 1009 and 1010**Step 1:

- 15 To a solution of phenol **3b6** (1.15 g, 2.85 mmol) and K_2CO_3 (0.59 g, 4.2 mmol) in anhydrous DMSO (20 mL) is added pyridine **5a4** (500 mg, 2.92 mmol). The resulting mixture is stirred at 100°C for about 30 min, then diluted with EtOAc and successively washed with water, brine and concentrated under reduced pressure. Following purification by silica gel column chromatography on a Combiflash (50% EtOAc in hex), **9a1** is isolated.
- 20

Step 2:

- $NaBH_4$ (0.11 g, 2.8 mmol) is added portionwise to a cold solution (0°C) of aldehyde **9a1** (1.10 g, 1.91 mmol) in MeOH. After being stirred for about 1 h, the reaction mixture is evaporated to dryness and redissolved in EtOAc. This mixture is successively washed with 10% aqueous solution of $NaHSO_4$, saturated aqueous
- 25

solution of NaHCO_3 and brine. The organics are dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude compound is purified by silica gel column chromatography on a Combiflash (50% EtOAc in Hex) to afford alcohol **9a2**.

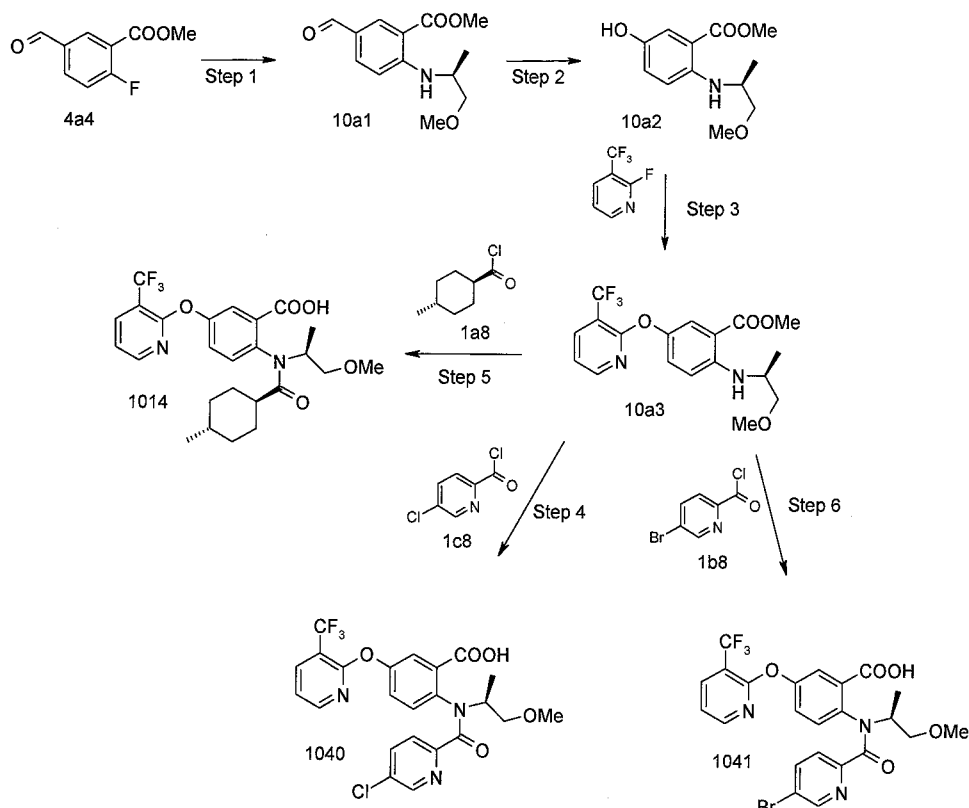
5 Step 3:

To a solution of alcohol **9a2** (1.0 g, 1.7 mmol) in anhydrous DCM (25 mL) is added thionyl chloride (0.25 mL, 3.4 mmol) followed by a catalytic amount of DMF (2 drops). The resulting solution is stirred for about 30 min at RT, diluted with DCM and washed with a saturated solution of NaHCO_3 and brine. The organics are dried over
10 Na_2SO_4 , filtered and concentrated to give chloride **9a3** which is directly used in the next step.

Step 4:

The chloride **9a3** (120 mg, 0.22 mmol) along with 1,2,3-triazole (17 mg, 0.25 mmol),
15 Cs_2CO_3 (124 mg, 0.38 mmol) and KI (16 mg, 0.099 mmol) are mixed in DMF (2 mL). The mixture is warmed to 70°C for about 2 h, then cooled down to RT. A solution of NaOH (2.5 N, 0.8 mL, 2 mmol) and DMSO (0.5 mL) is then added. The mixture is warmed to 50°C for about 1 h, neutralized at RT with AcOH and injected onto the preparative HPLC to isolate **1009** and **1010**.

20

EXAMPLE 10A**Preparation of compounds 1040, 1041 and 1014****Step 1:**

Potassium carbonate (400 mg, 2.89 mmol) is added to a DMSO (4.0 mL) solution of fluoride **4a4** (438 mg, 2.4 mmol) and (S)-(+)-1-methoxy-2-propylamine (858 mg, 9.63 mmol). The mixture is heated at 70°C for about 20 h, cooled to RT and diluted with water. Concentrated HCl is then added. The solution is stirred at RT for about 1 h, basified with aqueous 2.5 N NaOH and extracted with EtOAc. The organic phase is washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product **10a1** is used directly in the next step.

Step 2:

Hydrogen peroxide (374 µL, 3.3 mmol) is added to a 0°C MeOH (3.0 mL) solution of the aldehyde **10a1** and sulfuric acid (180 µL, 2.9 mmol). The solution is stirred at 0°C for about 2 h, basified with aqueous 2.5 N NaOH and extracted with EtOAc. The organic phase is washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography to afford phenol **10a2** as a yellow solid.

Step 3:

Potassium carbonate (829 mg, 6.0 mmol) is added to a DMSO (8.0 mL) solution of the phenol **10a2** (337 mg, 1.41 mmol) and 2-fluoro-3-(trifluoromethyl)pyridine (247 mg, 1.5 mmol). The mixture is stirred at 85°C for about 6 h then cooled to RT and
5 diluted with EtOAc. The organic phase is washed with aqueous saturated sodium bicarbonate, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography to afford ether **10a3** as a white solid.

10 Step 4:

Pyridine (100 µL) is added to a DCE (1 mL) solution of the aniline **10a3** (50 mg, 0.13 mmol) and the acid chloride **1c8** (105 mg, 0.60 mmol). The mixture is stirred at 150°C for 15 min in a microwave, cooled to RT and concentrated under reduced pressure. The residue is dissolved in DMSO (2.0 mL) and aqueous 2.5 N NaOH
15 (200 µL) is added. The reaction mixture is stirred at RT for about 2 h, acidified with AcOH and purified by preparative HPLC to afford **1040**.

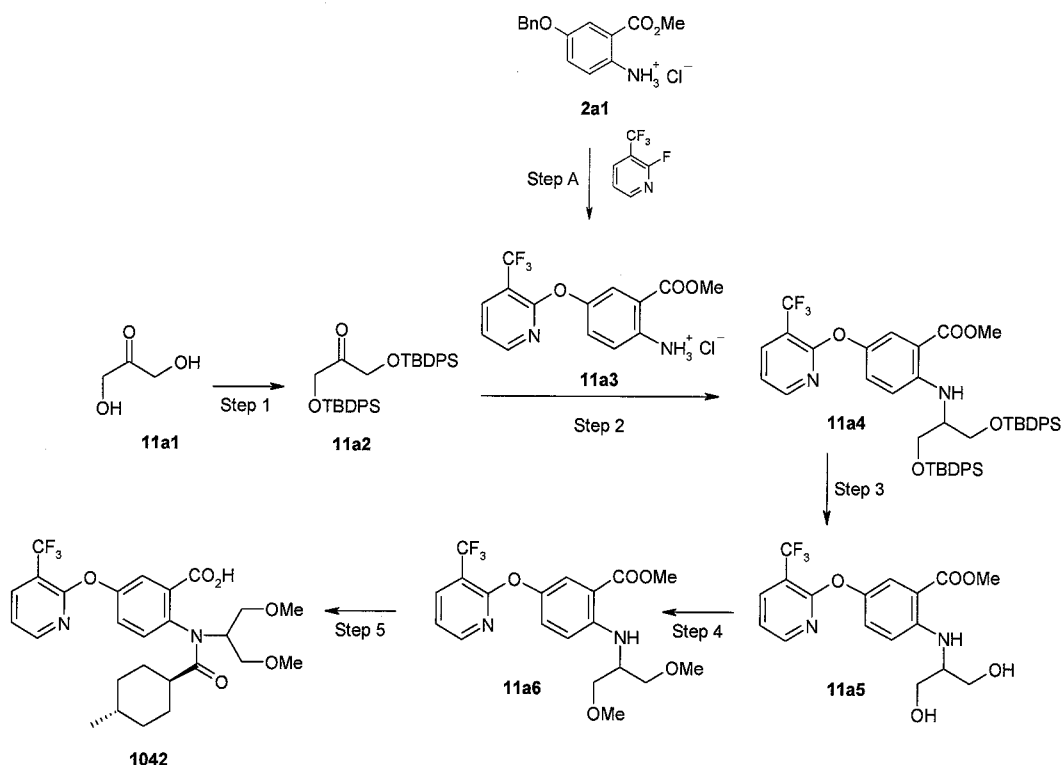
Step 5:

Pyridine (500 µL) is added to a DCE (1 mL) solution of the aniline **10a3** (490 mg, 1.27 mmol) and the acid chloride **1a8** (422 mg, 2.62 mmol). The mixture is stirred at
20 150°C for about 15 min in a microwave, cooled to RT and concentrated under reduced pressure. The residue is dissolved in DMSO (2.0 mL) and aqueous 2.5 N NaOH (200 µL) is added. The reaction mixture is stirred at RT for about 2 h, acidified with AcOH and purified by preparative HPLC to give **1014**.

25

Step 6:

Pyridine (40 µL) is added to a DCE (1 mL) solution of the aniline **10a3** (41 mg, 0.11 mmol) and the acid chloride **1b8** (48.8 mg, 0.22 mmol). The mixture is stirred at
30 150°C for 15 min in a microwave, cooled to RT and concentrated under reduced pressure. The residue is dissolved in DMSO (2.0 mL) and aqueous 2.5 N NaOH (200 µL) is added. The reaction mixture is stirred at RT for about 2 h, acidified with AcOH and purified by preparative HPLC to give **1041**.

EXAMPLE 11A**Preparation of compound 1042****Step A:**

- 5 Compound **2a1** is transformed to compound **11a3**, using the procedure in Steps 2 and 3, Example 8A.

Step 1:

- 10 1,3-dihydroxyacetone **11a1** (964 mg, 10.7 mmol) is dissolved in DCM (25 mL) and imidazole (2.19 g, 32.1 mmol) followed by *tert*-butyldiphenylchlorosilane (5.8 mL, 22.5 mmol) are added. The mixture is stirred at RT until the reaction is complete, then water is added. The layers are separated; the organics are dried over MgSO_4 , filtered and concentrated under reduced pressure to afford **11a2** which is used without further purification.

15

Step 2:

The hydrochloride aniline salt **11a3** (200 mg, 0.57 mmol) is dissolved in DCM (10 mL) along with ketone **11a2** (651 mg, 1.15 mmol). After being stirred for about 10 min, $\text{NaBH}(\text{OAc})_3$ (243 mg, 1.15 mmol) is added and the mixture is refluxed. The

mixture is neutralized by adding a saturated aqueous solution of NaHCO_3 ; then extracted with DCM (3x). The organics are washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography (2% EtOAc in hex) to give aniline **11a4**.

5

Step 3:

To a solution of compound **11a4** (674 mg, 0.78 mmol) in THF (10 mL) is added a solution of TBAF (1.0 M in THF, 1.6 mL, 1.6 mmol). The solution is stirred at RT until the reaction is complete, diluted with a saturated aqueous solution of NH_4Cl and
10 extracted with DCM (3x). The combined organics are washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Following purification by flash chromatography (2% to 8% MeOH in DCM), diol **11a5** is isolated.

Step 4:

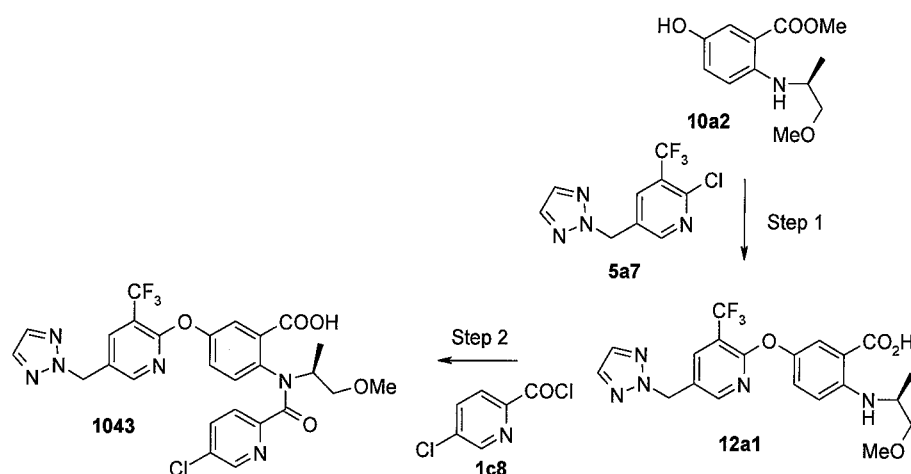
15 Diol **11a5** is transformed to dimethoxy **11a6** using the procedure of Step 5, Example 1A.

Step 5:

In a microwave tube, dimethoxy **11a6** (37 mg, 0.089 mmol) along with pyridine (36
20 μL , 0.45 mmol) and DMAP (1.1 mg, 9 μmol) are mixed in DCE (1 mL). The acid chloride **1a8** (91 mg, 0.57 mmol) is added and the tube is sealed and placed in a microwave at 175°C for 15 min. The mixture is diluted in EtOAc and washed with a saturated aqueous solution of NaHCO_3 (3x). The organics are dried over MgSO_4 and concentrated. The crude residue is re-dissolved in a THF (1 mL)/MeOH (0.5
25 mL)/ H_2O (0.5 mL) mixture and an aqueous NaOH solution (10 N, 45 μL , 0.45 mmol) is added. The mixture is stirred overnight before being acidified with AcOH, filtered then injected onto a preparative HPLC to isolate compound **1042**.

EXAMPLE 12A

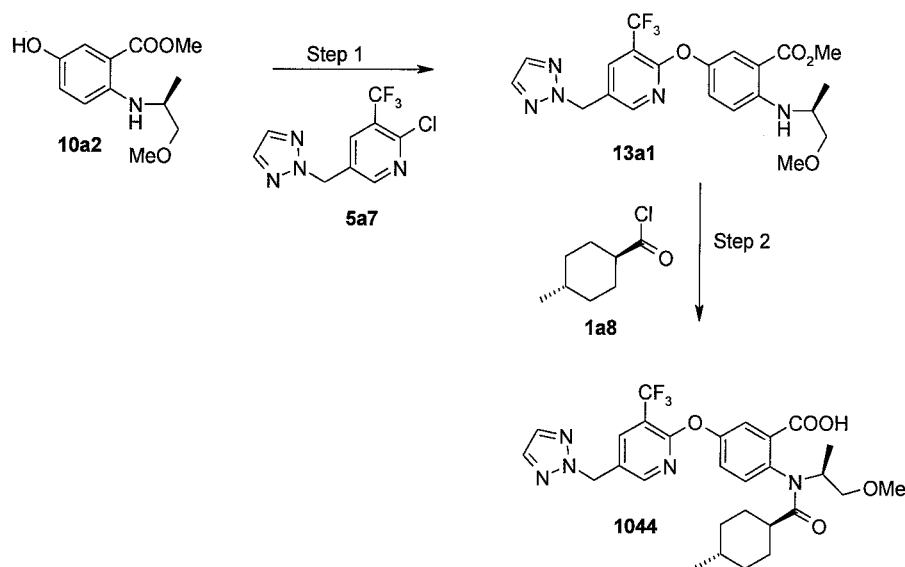
Preparation of compound 1043

Step 1:

- 5 Potassium carbonate (193 mg, 1.40 mmol) is added to a DMSO (6.0 mL) solution of phenol **10a2** (136.6 mg, 0.571 mmol) and chloropyridine **5a7** (150 mg, 0.571 mmol). The mixture is stirred at 80°C for about 12 h, cooled to RT and aqueous 2.5 N NaOH (0.90 mg, 2.25 mmol) is added. The solution is stirred at RT for about 1 h, diluted with water and acidified with AcOH. The solid is filtered and dried to afford the acid **12a1**
- 10 as a beige solid.

Step 2:

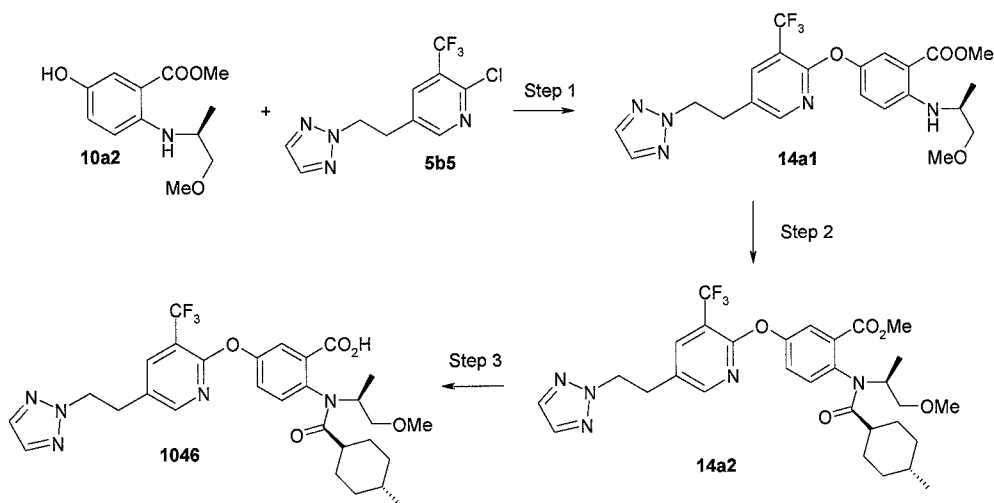
- Pyridine (49 µL) is added to a DCE (1 mL) solution of aniline **12a1** (60 mg, 0.133 mmol) and the acid chloride **1c8** (47.5 mg, 0.270 mmol). The mixture is stirred at
- 15 150°C for 15 min in a microwave, cooled to RT, acidified with AcOH and purified by preparative HPLC to afford **1043**.

EXAMPLE 13A**PREPARATION OF COMPOUND 1044****Step 1:**

- 5 Potassium carbonate (650 mg, 4.703 mmol) is added to a DMSO (15.0 mL) solution of phenol **10a2** (456.0 mg, 1.906 mmol) and chloropyridine **5a7** (500 mg, 1.904 mmol). The mixture is stirred at 80°C for about 12 h, cooled to RT and diluted with EtOAc. The organic phase is washed with aqueous saturated sodium bicarbonate, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The
- 10 crude residue is purified by column chromatography (30% EtOAc in hexanes) to afford triazole **13a1**.

Step 2:

- Pyridine (404 µL, 5.0 mmol) is added to a DCE (1 mL) solution of aniline **13a1** (433 mg, 0.930 mmol) and acid chloride **1a8** (450 mg, 2.801 mmol). The mixture is stirred
- 15 at 140°C for 60 min in a microwave, cooled to RT and concentrated under reduced pressure. The residue is dissolved in MeOH/THF (1:2) and aqueous 1 N NaOH (660 µL) is added. The mixture is stirred at RT for about 2 days, acidified with aqueous HCl and purified by preparative HPLC to afford **1044**.

EXAMPLE 14A**Preparation of compound 1046****Step 1:**

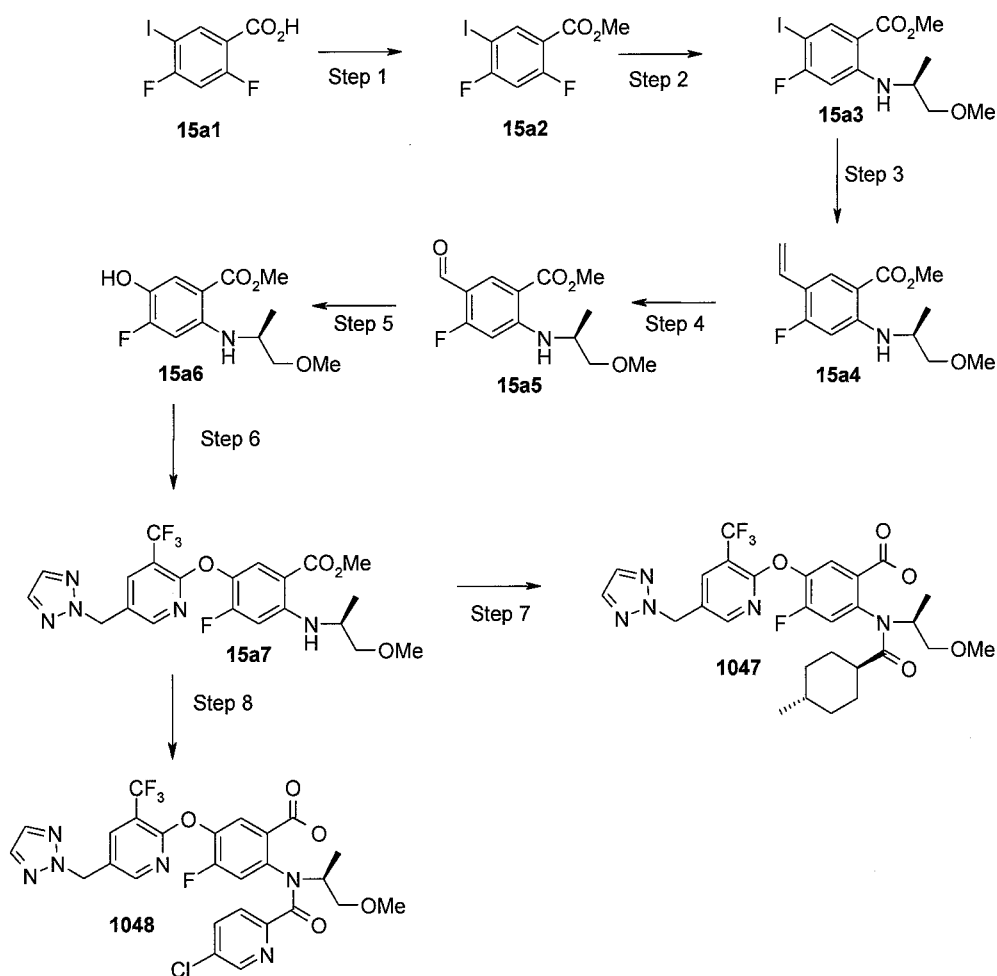
- 5 Compound **14a1** is generated via a reaction between compounds **10a2** and **5b5** using the procedure of Step 1, Example 13A.

Step 2:

- 10 Compound **14a1** is transformed to compound **14a2** using the procedure of Step 5, Example 11A.

Step 3:

- 15 To a solution of **14a2** (190 mg, 0.32 mmol) in MeCN/deionized water is added aqueous NaOH (0.32 mL, 1 M). This is stirred at RT for about 96 h. An additional amount of aqueous NaOH (0.64 mL, 1 M) is added and the resulting solution is allowed to stir for about 18 h. A 1 M HCl solution in water is added at 0°C until acidic pH. The solution is extracted with EtOAc (4x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. A light yellow oil (194 mg) is obtained which is dissolved in
- 20 MeCN/deionized water (100 mL, 1:1) and 1 equivalence of 1 M aqueous NaOH is added. The solvent is then removed by lyophilization (~2 days) to yield **1046**.

EXAMPLE 15A**Preparation of compound 1047 and 1048****5 Step 1:**

Sulfuric acid (1 mL) is added to a solution of acid **15a1** (5.00 g, 17.6 mmol) in MeOH (100 mL). The solution is stirred overnight at 80°C. The mixture is cooled to RT, concentrated under reduced pressure, diluted with EtOAc (300 mL), washed with saturated aqueous NaHCO₃ (3 x 100 mL), brine (100 mL), dried over Na₂SO₄,
 10 filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography (100% hexanes then 5% to 10% EtOAc in hexanes) to afford methyl ester **15a2** as an oil that solidifies upon standing under high vacuum.

Step 2

15 (S)-(+)-1-methoxy-2-propylamine (1.47 g, 16.7 mmol) is added to a DMF (30 mL) solution of fluoride **15a2** (3.30 g, 11.1 mmol) and potassium carbonate (2.28 g, 16.7

mmol). The mixture is stirred at 90°C overnight, cooled to RT, diluted with saturated aqueous NaHCO₃ (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with saturated aqueous NaHCO₃ (2 x 100 mL), brine (100 mL) dried over Na₂SO₄, filtered and concentrated under reduced pressure. The
5 crude mixture is purified by flash chromatography (100% hexanes then 5% to 20% EtOAc in hexanes) to afford amine **15a3** as an oil.

Step 3:

Pd(PPh₃)₄ (774 mg, 0.67 mmol) is added to a mixture of iodide **15a3** (2.46 g, 0.670
10 mmol) and tributylvinyltin (2.2 mL, 0.73 mmol) in DMF (30 mL). The mixture is degassed by simultaneously bubbling Ar and sonicating the solution for about 15 min. The mixture is stirred at 110°C for about 2.5 h, cooled to RT, diluted with saturated aqueous NaHCO₃ (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with saturated aqueous NaHCO₃ (2 x 100
15 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by flash chromatography (100% hexanes then 5% to 10% EtOAc in hexanes) to afford vinyl compound **15a4** as an oil.

Step 4:

Vinyl compound **15a4** (1.00 g, 3.75 mmol) is dissolved in a mixture of acetone/*tert*-butanol/water (20 mL : 8 mL : 4 mL). The solution is cooled to 0°C, NMO (572 mg, 5.62 mmol) is added, followed by OsO₄ (2.5% in *tert*-butanol, 1.96 mL, 0.18 mmol). The solution is stirred at 0°C for about 2 h, diluted with aqueous 10% sodium thiosulphate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined
25 organic phases are washed with aqueous 10% thiosulphate (100 mL), brine (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude diol which is dissolved in THF (30 mL) and water (15 mL). This solution is cooled to 0°C and NaIO₄ is added (1.2 g, 5.6 mmol). The solution is stirred at 0°C for about 4 h. The reaction mixture is diluted with saturated aqueous NaHCO₃ (100 mL)
30 and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by flash chromatography (100% hexanes then 5% to 20% EtOAc in hexanes) to afford aldehyde **15a5** as an oil.

Step 5:

Sulfuric acid (0.162 mL, 2.6 mmol) is added to a 0°C MeOH (10 mL) solution of aldehyde **15a5** (500 mg, 1.86 mmol), followed by aqueous 30% hydrogen peroxide (0.295 mL, 2.6 mmol). The solution is stirred at 0°C for about 1 h then diluted with aqueous 10% KH₂PO₄ (50 mL) and extracted with ether (2 x 100 mL). The combined organic phases are washed with aqueous 10% KH₂PO₄ (2 x 100 mL), brine (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude phenol **15a6** is used directly in the next step without further purification.

10 Step 6:

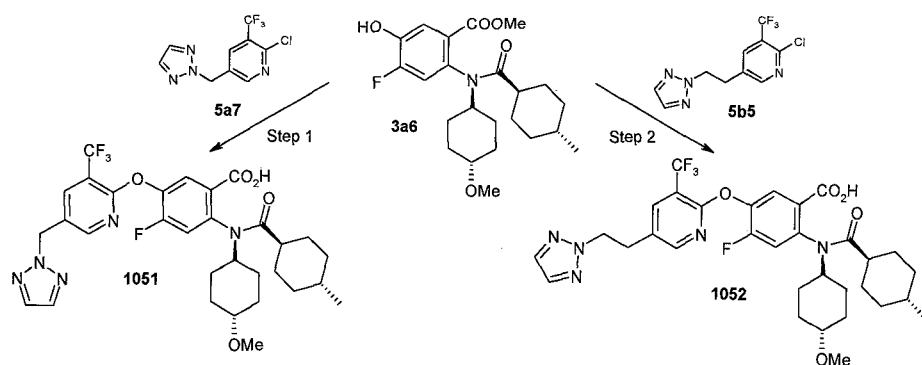
Phenol **15a6** is transformed to triazole **15a7** using the procedure described in Step 1, Example 13A.

Step 7:

15 Amine **15a7** is transformed to compound **1047** using the procedure described in Step 2, Example 13A.

Step 8:

20 Amine **15a7** is transformed to compound **1048** using the procedure described in Step 4, Example 10A

EXAMPLE 16A**Preparation of compounds 1051 and 1052**

25

Step 1:

To a solution of phenol **3a6** (701 mg, 1.66 mmol) and Cs₂CO₃ (737 mg, 2.27 mmol) in anhydrous DMSO (8 mL) is added chloropyridine **5a7** (397 mg, 1.51 mmol). The

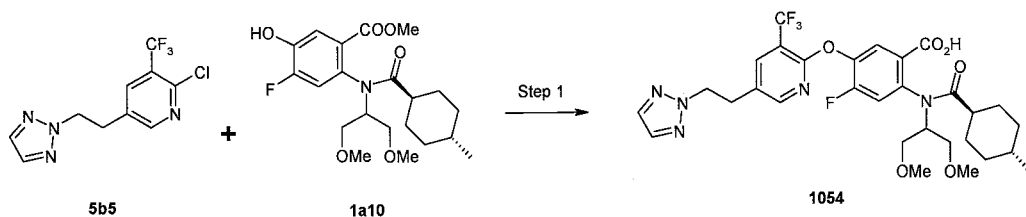
resulting mixture is stirred at 80°C for about 2 h, then diluted with EtOAc and successively washed with water, brine and concentrated under reduced pressure. Following purification by combiflash (15% EtOAc in hex), the intermediate methyl ester is isolated. This ester is redissolved in a THF (20 mL)/MeOH (10 mL) mixture and an aqueous NaOH solution (10 N, 0.8 mL, 8.0 mmol) is added. The mixture is stirred overnight before being acidified with AcOH, filtered, and injected onto a preparative HPLC. The combined fractions are lyophilized and the solid is dissolved in EtOAc. This organic solution is washed with 1 M NaOH (3x). The combined aqueous fractions are acidified with 1 M HCl until ~pH 6 and extracted with EtOAc (3x). The organics are dried over MgSO₄ and concentrated. The product is redissolved in MeCN and water and lyophilized to afford **1051**.

Step 2:

The coupling of phenol **3a6** with pyridine **5b5** is performed as described previously in Step 1, Example 16A. The saponification of the crude methyl ester (0.18 mmol) is performed in MeOH (1 mL) with NaOH (1 M, 0.9 mL, 0.9 mmol). Following complete conversion, the mixture is acidified with AcOH, filtered, then injected onto a preparative HPLC to afford **1052**.

20 EXAMPLE 17A

Preparation of compound 1054



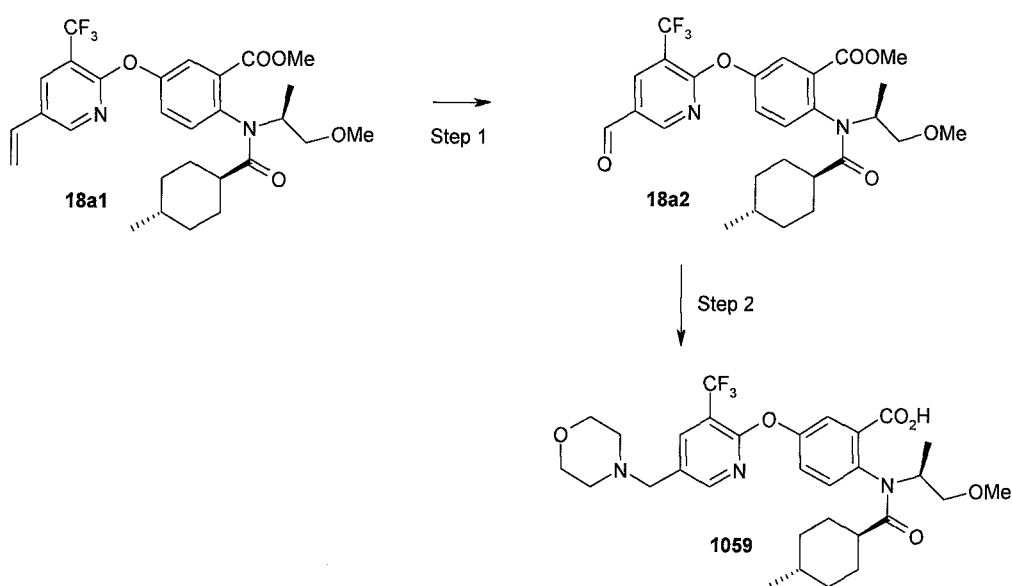
Step 1:

To a solution of phenol **1a10** (1.96 g, 4.77 mmol) and Cs₂CO₃ (1.83 g, 5.64 mmol) in anhydrous DMSO (30 mL) is added pyridine **5b5** (1.20 g, 4.34 mmol). The resulting mixture is stirred at 95°C overnight, then poured in water and extracted with Et₂O (3x). The combined organic fractions are concentrated under reduced pressure. Following purification by combiflash (10% to 50% EtOAc in hex), the intermediate methyl ester is isolated. This ester is redissolved in MeOH (2 mL) and an aqueous NaOH solution (1 N, 2.34 mL, 2.34 mmol) is added. The mixture is stirred overnight before being washed with Et₂O, then acidified at 0°C with 1 M HCl and extracted with

EtOAc (4x). The combined fractions are dried and concentrated. The product is triturated (3x) with a pentane / Et₂O (3:1) mixture, dissolved in MeCN and water and lyophilized to afford **1054** as the sodium salt.

5 EXAMPLE 18A

Preparation of compound 1059



Step 1:

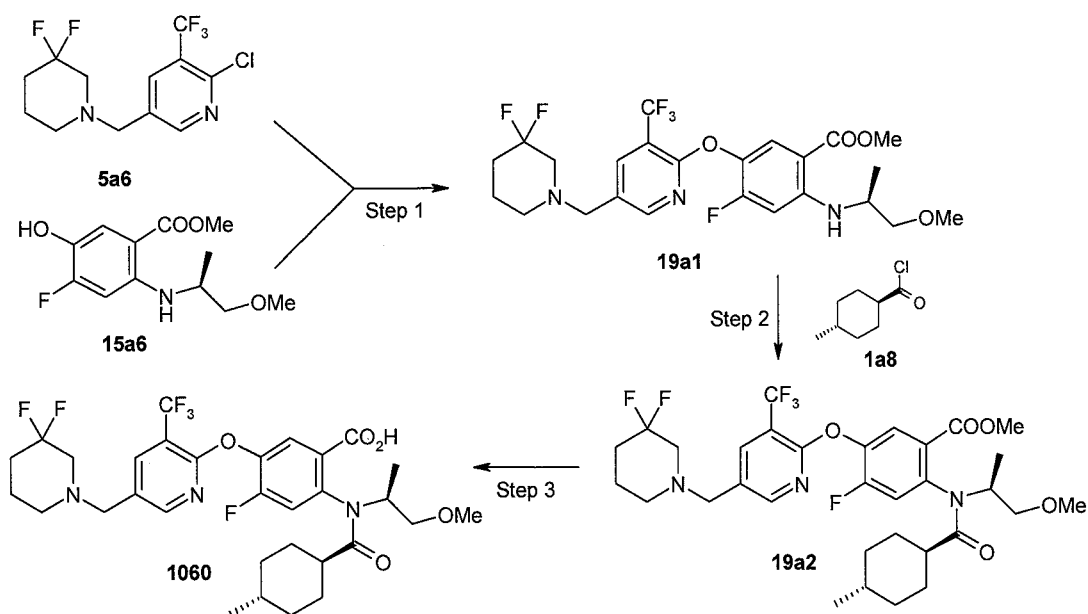
- 10 Vinyl compound **18a1** (prepared according to the same procedure described in Step 2, Example 25A) is transformed to aldehyde **18a2** using the procedure in Step 4, Example 15A.

Step 2:

- 15 To a solution of aldehyde **18a2** (60 mg, 0.11 mmol) in DCM (1 mL) is sequentially added morpholine (34 μ L, 0.56 mmol), a solution of HCl (4 M in dioxane, 28 μ L, 0.11 mmol) and NaBH(OAc)₃ (47 mg, 0.22 mmol). The reaction is stirred at RT, then concentrated to dryness. The mixture is re-dissolved in MeOH (1 mL) and NaOH (10 N, 0.1 mL, 1 mmol) is added. When complete, the reaction is neutralized with AcOH
- 20 and injected onto the preparative HPLC to isolate **1059**.

EXAMPLE 19A

Preparation of compound 1060

**Step 1:**

Compound **19a1** is generated via a reaction between compounds **5a6** and **15a6**

5 using the procedure of Step 1, Example 16A.

Step 2:

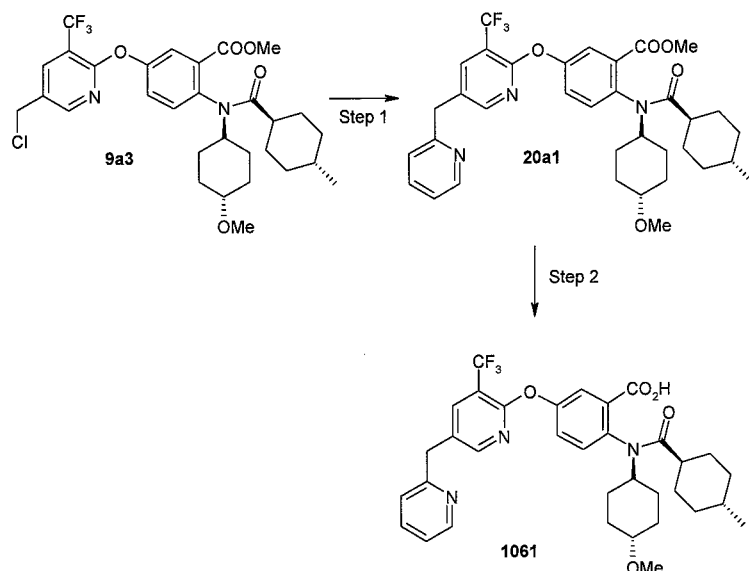
In a microwave tube, the intermediate **19a1** (75 mg, 0.14 mmol) is dissolved in pyridine (1 mL) and a solution of acid chloride **1a8** (2 M in DCE, 0.5 mL, 0.90 mmol) is then added followed by a catalytic amount of DMAP (7 mg, 56 μ mol). The tube is sealed and put in microwave at 150°C for 20 min. The mixture is diluted in EtOAc and washed with water (2x) and brine (1x). The combined organics are dried over MgSO_4 , filtered and concentrated. The crude residue is purified by flash chromatography (5% to 70% EtOAc in hex) to afford **19a2**.

15

Step 3:

Methyl ester **19a2** (16 mg, 24 μ mol) is dissolved in a 2:1 THF/MeOH mixture (0.5 mL) and an aqueous NaOH solution (1.0 M, 25 μ L, 25 μ mol) is then added. The reaction is stirred at RT, diluted in water and the aqueous layer is washed with Et_2O (2x) to remove organic impurities. The aqueous fraction is lyophilized and the compound **1060** is isolated as its sodium salt.

20

EXAMPLE 20A**Preparation of compound 1061****5 Step 1:**

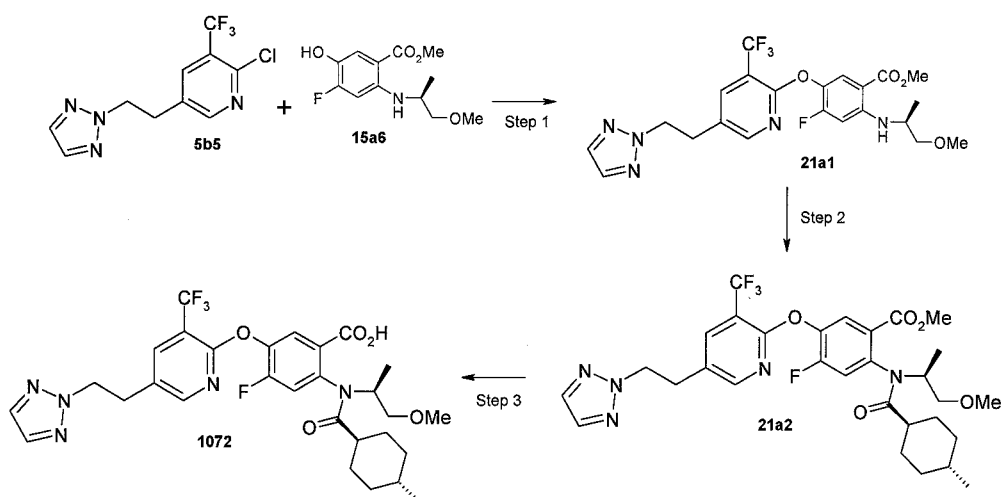
In a microwave tube, the chloride **9a3** (60 mg, 0.10 mmol) is dissolved in degassed DMF (2 mL, degassed by bubbling Ar while sonicating for about 10 min). 2-(tributylstannyl)pyridine (92 mg, 0.25 mmol) and Pd(PPh₃)₄ catalyst (12 mg, 10 μmol) are then added. The mixture is further degassed and the tube is sealed and put in
 10 microwave at 120°C for 20 min. The mixture is diluted in EtOAc and washed with water (2x) and brine (2x). The combined organics are dried over MgSO₄, filtered and concentrated. The crude residue is purified by flash chromatography (25% to 75% EtOAc in hex) to afford **20a1**.

15 Step 2:

The intermediate **20a1** (35 mg, 0.055 mmol) is dissolved in a THF (3 mL)/MeOH (0.5 mL)/H₂O (0.5 mL) mixture and an aqueous NaOH solution (10 N, 27 μL, 0.27 mmol) is added. When complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate **1061**.

20

EXAMPLE 21A**Preparation of compound 1072**

**Step 1:**

Compound **21a1** is generated via a reaction between compounds **5b5** and **15a6**
 5 using the procedure of Step 1, Example 13A.

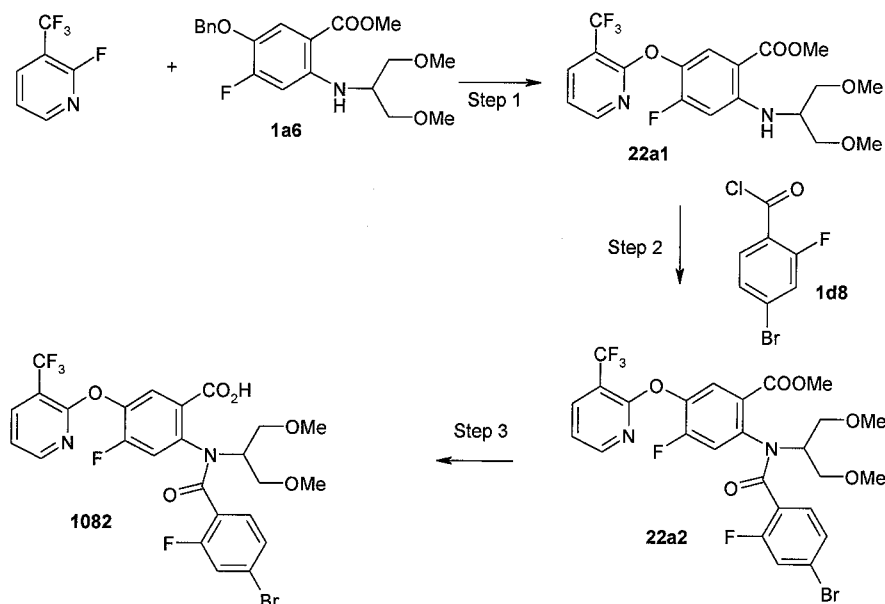
Step 2:

Compound **21a1** is transformed to compound **21a2** using the procedure of Step 5,
 Example 11A.

10

Step 3:

Compound **21a2** is transformed to compound **1072** using the procedure of Step 3,
 Example 14A.

EXAMPLE 22A**Preparation of compound 1082****5 Step 1:**

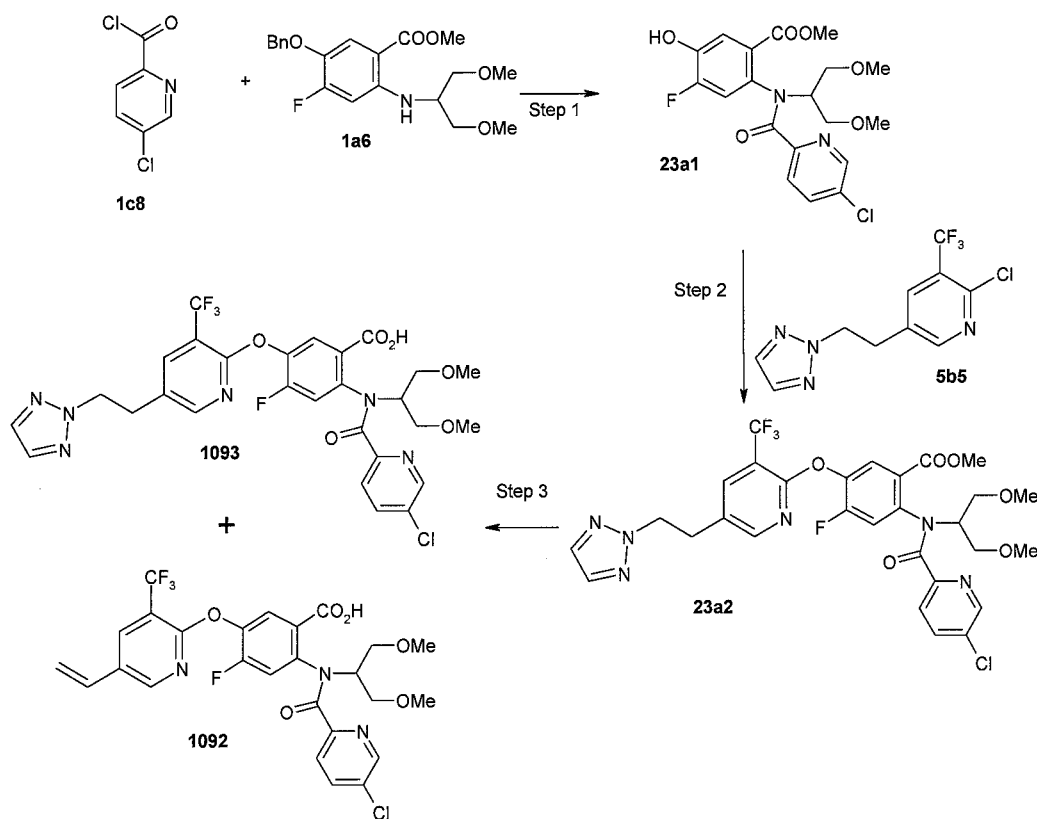
Compound **22a1** is generated via the reaction of compound **1a6** and 2-fluoro-3-trifluoromethylpyridine using the procedures of Steps 2 and 3, Example 8A.

Step 2:

- 10 In a 25 mL flask is added **22a1** (60 mg, 0.14 mmol), pyridine (0.25 mL, 3.1 mmol), acylchloride **1d8** (99 mg, 0.42 mmol) and DMAP (5.1 mg, 0.04 mmol). This mixture is heated to 150°C for about 4 h and then cooled and stirred at RT for about 65 h. This is quenched with NaHCO₃ (saturated), extracted with DCM (3x), passed through a phase separator and concentrated under reduced pressure to obtain crude product
- 15 **22a2** which is employed in the subsequent step without further purification.

Step 3:

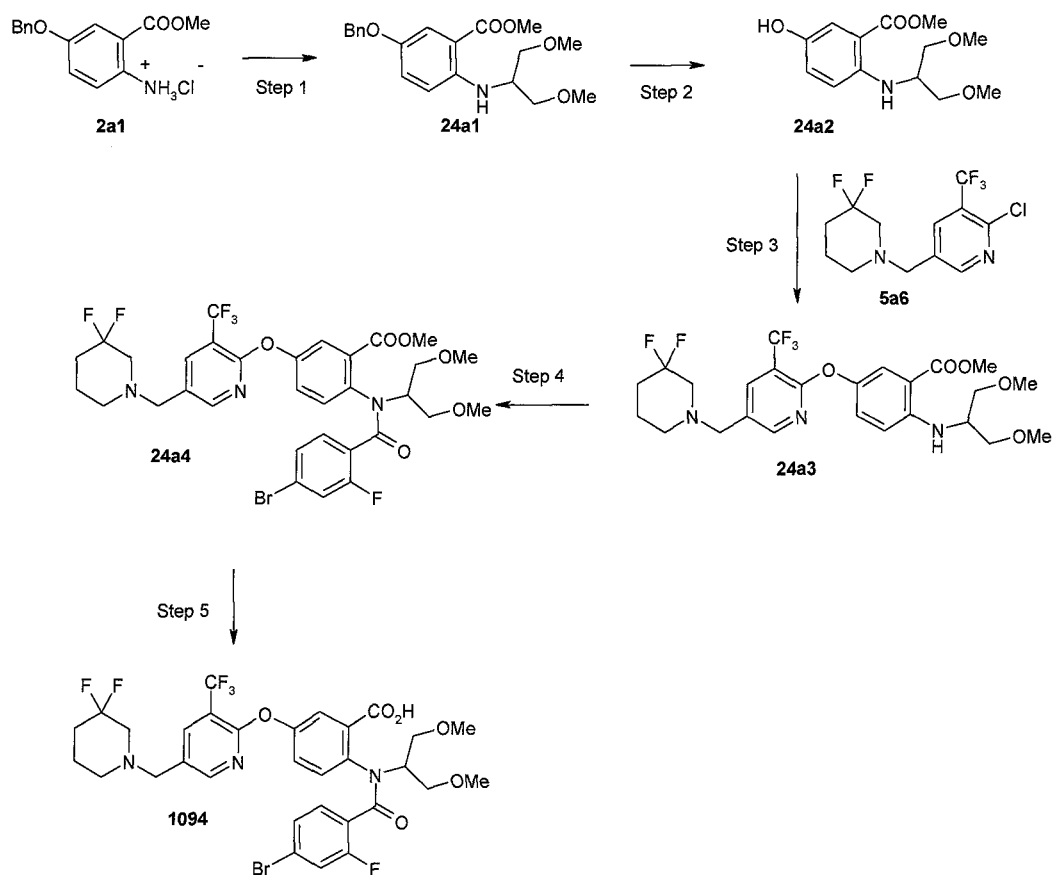
- Compound **22a2** is dissolved in THF/MeOH/H₂O (2:1:1 mL), NaOH (10 M, 0.07 mL) is added and the reaction is stirred for about 36 h at RT. A minimum amount of
- 20 aqueous AcOH is added to neutralize the solution and the solvent is evaporated. Purification by preparative HPLC affords compound **1082** as a white lyophilized solid.

EXAMPLE 23A**Preparation of compounds 1092 and 1093****5 Step 1:**

Compounds **1c8** and **1a6** are reacted using the procedure in Step 2, Example 19A. The deprotection of the benzyl ether is performed employing the same procedure as that in Step 2, Example 8A to produce compound **23a1**.

10 Steps 2 and 3:

To a solution of phenol (50 mg, 0.12 mmol) in DMSO (1 mL) is added CsCO₃ (57 mg, 0.18 mmol) followed by chloropyridine **5b5** (90 mg, 0.33 mmol). This is stirred at 105°C for about 18 h, then cooled to RT. MeOH (1 mL), NaOH (1 eq, 1 M in water) and LiOH (1 eq) are added and this is stirred for about 4 h at RT. The mixture is then concentrated, diluted in AcOH (4 mL) and purified by preparative HPLC. The fractions are combined and solvent is removed by lyophilization to yield two products, **1093** and **1092**.

EXAMPLE 24A**Preparation of compound 1094****5 Step 1:**

Compound **2a1** is transformed to compound **24a1** using the procedure in Steps 4 and 5, Example 1A.

Step 2:

- 10 Compound **24a1** is transformed to compound **24a2** using the procedure in Step 8, Example 1A.

Step 3:

- 15 Compounds **24a2** and **5a6** are combined to form compound **24a3** using the procedure in Step 3, Example 8A.

Steps 4 and 5:

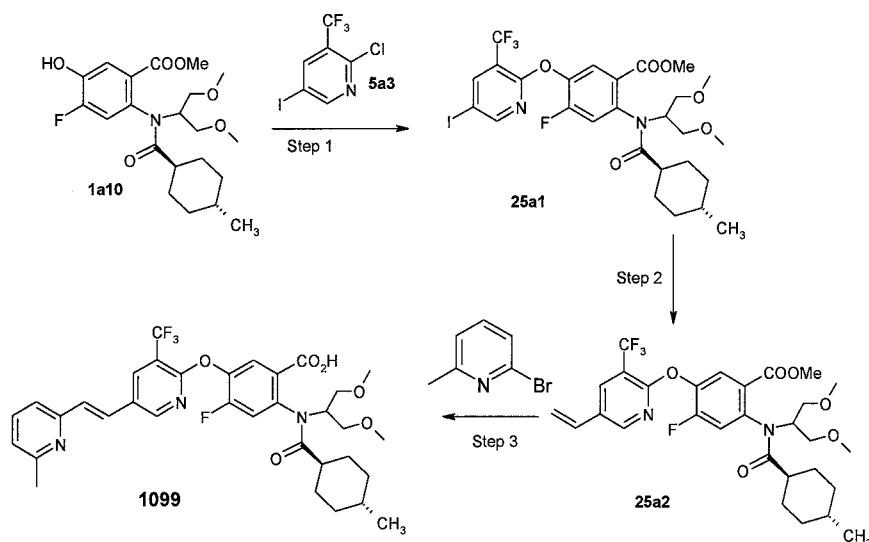
Compound **24a3** is transformed to **24a4** and thereafter to compound **1094** using the

procedure in Steps 2 and 3, Example 22A, respectively.

EXAMPLE 25A

Preparation of compound 1099

5



Step 1:

To a solution of phenol **1a10** (400 mg, 0.97 mmol) in DMSO (5 mL) is added CsCO₃ (474 mg, 1.4 mmol) and chloropyridine **5a3** (430 mg, 1.40 mmol). The solution is stirred at 75°C for about 4 h and then washed with water and brine. The solution is then dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated under reduced pressure. Purification by flash chromatography using (20:80 to 60:40) EtOAc/Hex yields **25a1**.

15

Step 2:

To a solution of iodide **25a1** (370 mg, 0.54 mmol) in dioxane (4 mL) is added tributyl(vinyl)tin (0.2 mL, 0.69 mmol) at RT. Argon is bubbled through the solution followed by the addition of dichloro-bis(triphenylphosphine)palladium (42 mg, 0.06 mmol). The reaction mixture is heated at reflux for about 1 h; then concentrated and purified by flash chromatography using (10:90 to 70:30) EtOAc/Hex to obtain **25a2**.

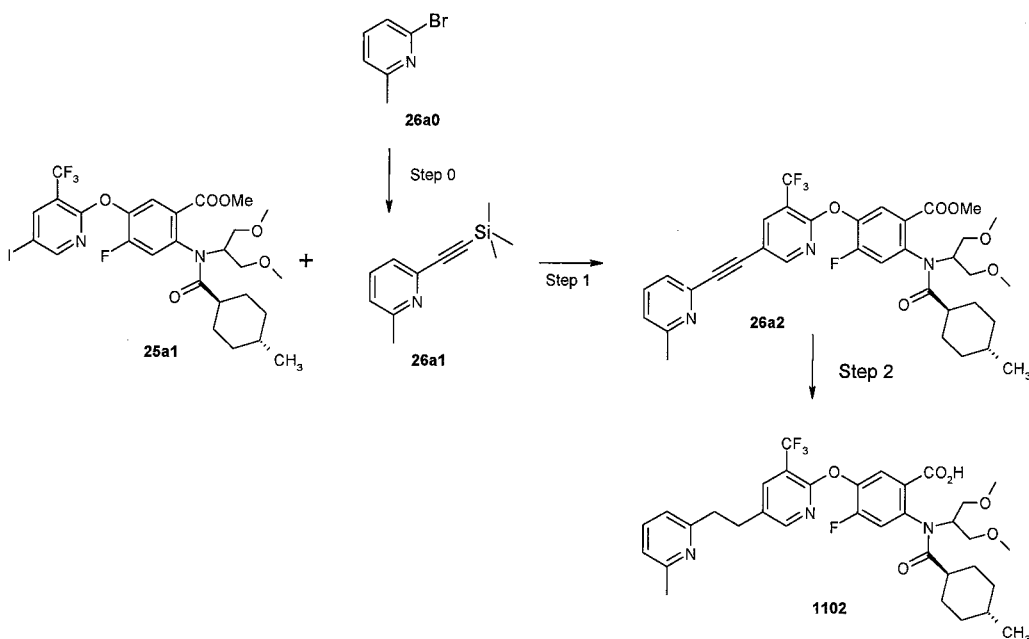
Step 3:

To a solution of olefin **25a2** (40 mg, 0.07 mmol) in DMF (1 mL) is added bromopyridine (18 mg, 0.10 mmol), TBABr (35 mg, 0.21 mmol), Et₃N (0.014 mL, 0.10

mmol) and palladium acetate (1.5 mg, 0.007 mmol) at RT. This is stirred at 120°C in the microwave for 10 min followed by heating at 140°C (oil bath) for about 16 h. The reaction mixture is quenched with water and extracted with EtOAc (3x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. THF (2 mL), MeOH (1 mL) and NaOH (1 M in water, 5 eq) are added and then this is stirred for about 14 h at RT. The reaction mixture is diluted with AcOH (1 mL) and purified by preparative HPLC. The fractions are combined and solvent is removed by lyophilization to yield **1099**.

10 EXAMPLE 26A

Preparation of compound 1102



15 Step 0:

In a microwave tube containing DMF (2 mL) is added 2-bromo-6-methylpyridine (300 mg, 1.74 mmol), trimethylsilylacetylene (257 mg, 2.62 mmol), CuI (33 mg, 0.17 mmol), Pd(PPh₃)₄ (201 mg, 0.17 mmol) and Et₃N (1.2 mL). The tube is sealed and placed in microwave for 10 min at 120°C. The mixture is then diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The crude residue is purified by flash chromatography (Hex / EtOAc, 20% to 80%) to afford pyridine **26a1**.

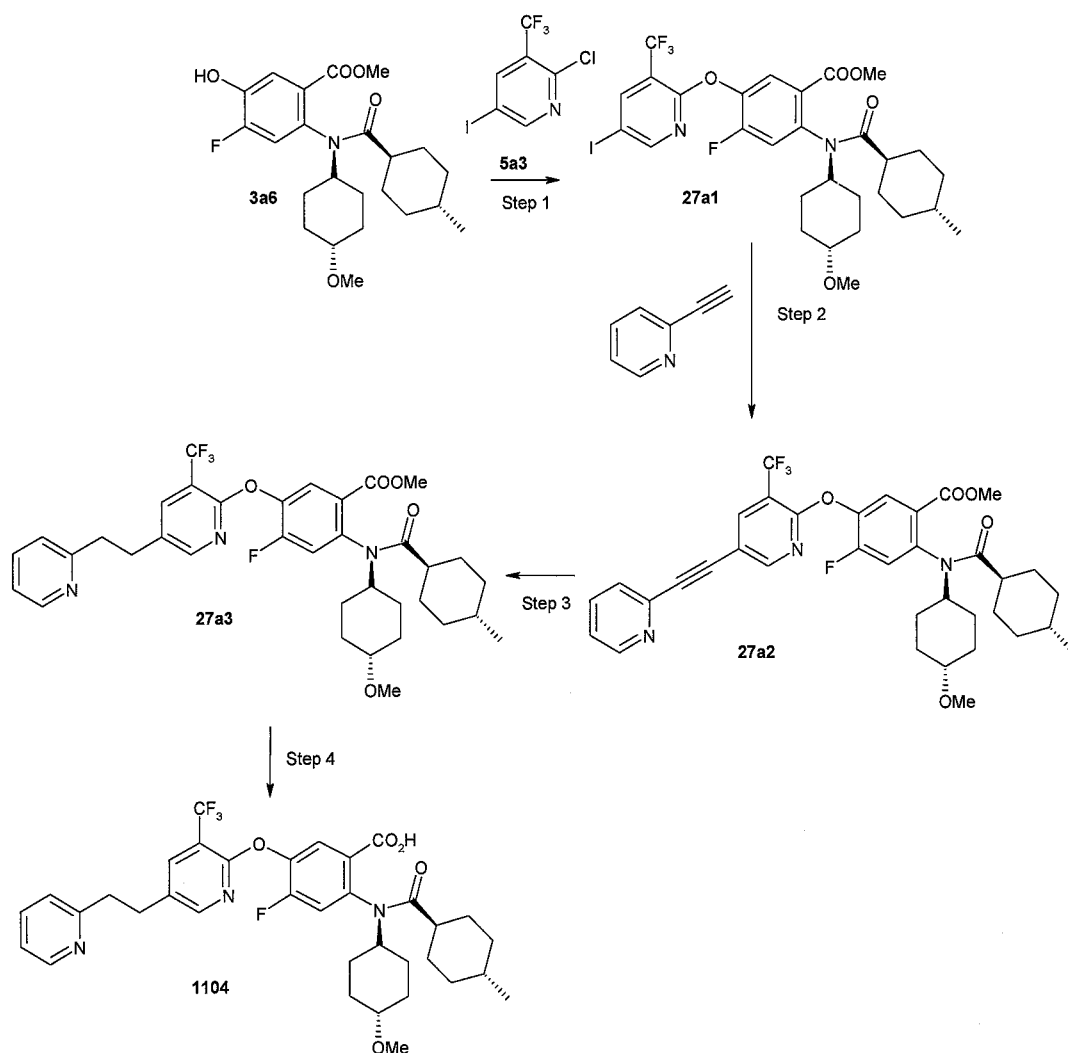
Step 1:

To a solution of alkyne **26a1** (33 mg, 0.18 mmol) in DMF (1 mL) is added TBAF (0.18 mL, 1 M solution in THF) at RT. This is stirred for about 10 min, then iodide
5 **25a1** (40 mg, 0.06 mmol), CuI (1.1 mg, 0.006 mmol), Et₃N (0.04 mL, 0.3 mmol) and Pd(PPh₃)₄ (6.8 mg, 0.006 mmol) are added at RT. This mixture is stirred at 120°C in the microwave for 12 min. The reaction mixture is quenched with water and extracted with EtOAc (3x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. Purification
10 by flash chromatography using (40:60 to 90:10) EtOAc/Hex affords **26a2**.

Step 2:

Compound **26a2** is dissolved in MeOH, Pd/C (10% w/w, 33 mg) is added and the mixture is purged with H₂ (3x). The mixture is stirred under a H₂ atmosphere
15 (balloon) for about 1 h, filtered and concentrated under reduced pressure. The residue is dissolved in MeOH and NaOH (1 M in water, 1 mL) is added followed by LiOH (3 eq). This mixture is stirred at RT for 2 h, concentrated, dissolved in AcOH (2 mL) and purified by preparative HPLC. The fractions are combined and solvent is removed by lyophilization to yield compound **1102**.

20

EXAMPLE 27A**Preparation of compound 1104****Step 1:**

Compound **3a6** is transformed to compound **27a1** using the procedure in Step 1,
 5 Example 13A.

Step 2:

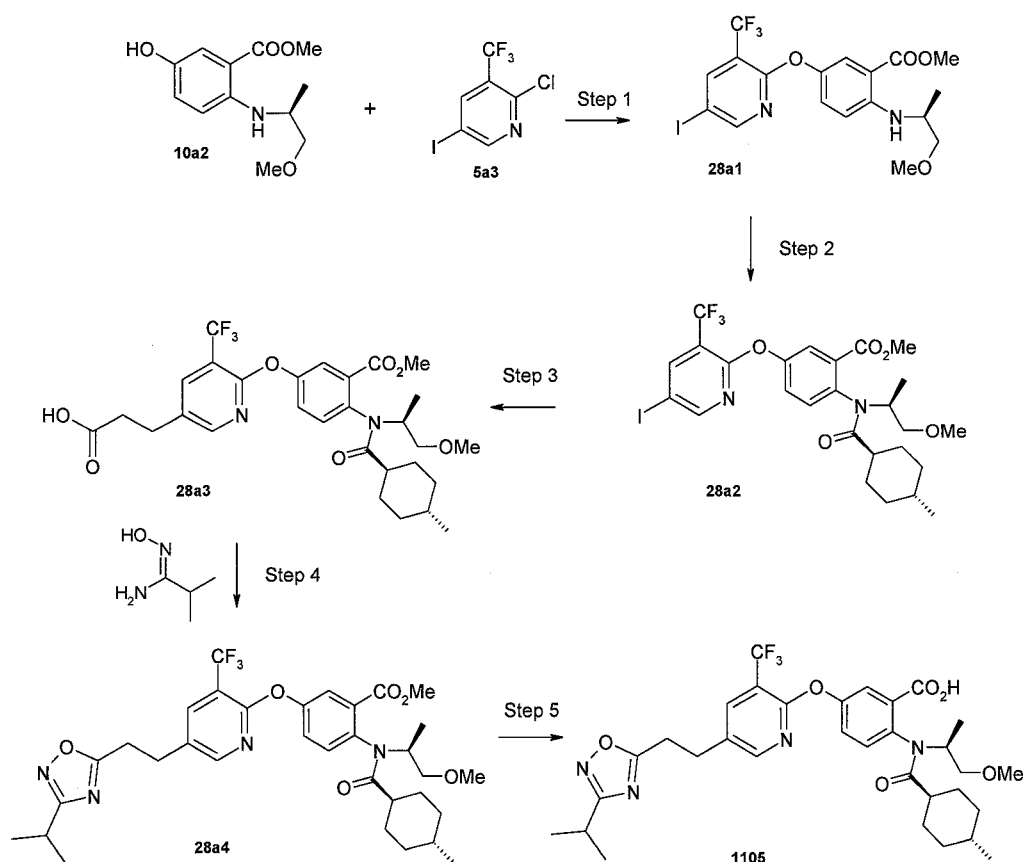
A mixture of iodide **27a1** (90 mg, 0.13 mmol), ethynylpyridine (27 mg, 0.26 mmol),
 CuI (2.5 mg, 0.013 mmol), Pd(PPh₃)₄ (15 mg, 0.013 mmol) and Et₃N (0.09 mL, 0.7
 10 mmol) in degassed DMF is heated in a microwave at 120°C for 20 min. This mixture
 is dissolved in EtOAc (50 mL), washed with water and brine, dried (MgSO₄) and
 concentrated. Purification by flash chromatography (1/2 then 1/1 EtOAc/Hex) yields
27a2 as pale yellow foam.

Step 3:

To the alkyne **27a2** (70 mg, 0.10 mmol) in MeOH (2 mL) is added Pd/C catalyst (10% w/w, 70 mg) which is then hydrogenated with ~15 psi of H₂ at RT for about 2.5 h. The catalyst is filtered and the residue is concentrated to dryness. The crude product **27a3** is isolated and employed in the subsequent reaction without further purification.

Step 4:

To the solution of the ester **27a3** (68 mg, 0.10 mmol) dissolved in DMSO (2 mL), MeOH (1 mL) and water (0.3 mL) is added at RT an aqueous solution of NaOH (10 N, 0.06 mL). This is stirred at RT for about 5 h and then maintained at 0°C overnight. The reaction is quenched with aqueous TFA and purified by preparative HPLC. The fractions are combined and lyophilized to yield **1104**.

15 EXAMPLE 28A**Preparation of compound 1105**

Step 1:

Compound **28a1** is generated through the reaction of compound **10a2** with compound **5a3** using the procedure of Step 1, Example 13A.

5 Step 2:

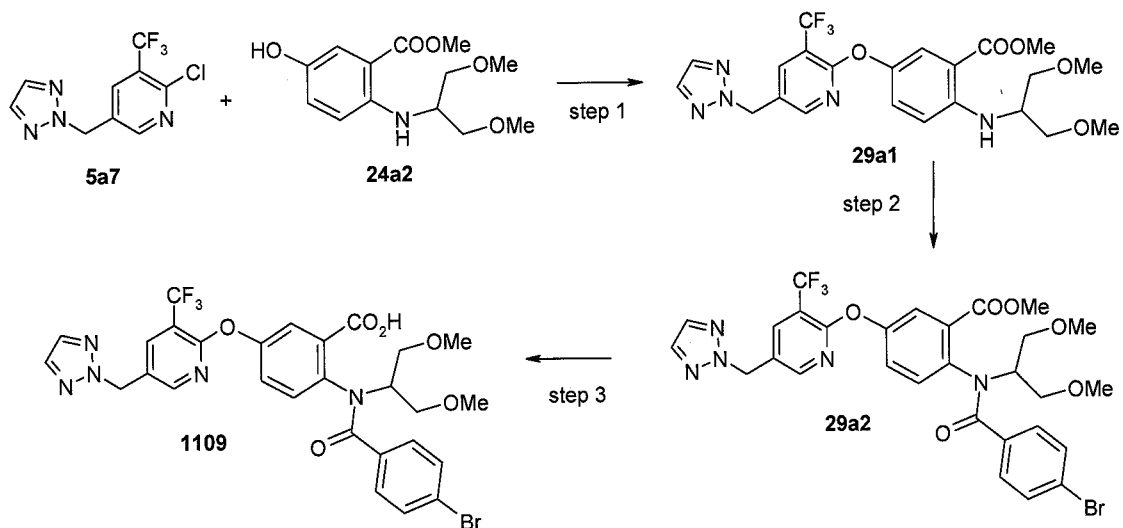
Compound **28a1** is transformed to compound **28a2** using the procedure of Step 5, Example 11A.

Step 3:

- 10 A mixture of iodide **28a2** (500 mg, 0.79 mmol), benzyl acrylate (1.3 g, 7.9 mmol), Pd(OAc)₂ (50 mg, 0.23 mmol), Et₃N (5.0 mL) and MeCN (20 mL) is stirred at 60°C in a sealed tube for about 4 h. The reaction mixture is cooled to RT, filtered and concentrated. Purification by flash chromatography (7:3 to 1:1 Hex:EtOAc) affords an oil which is taken up in EtOH (20 mL). Pd/C (10%, 50 mg) is added and then stirred
- 15 under H₂ for about 30 min. The reaction mixture is filtered on Celite® and concentrated to give **28a3** as a white foam.

Steps 4 and 5:

- To the acid **28a3** (50 mg, 0.09 mmol) in DMF (2.0 mL) is added Et₃N (0.06 mL, 0.4 mmol), and HATU (40 mg, 0.11 mmol). The reaction is stirred for about 10 min; then
- 20 amidooxime (8.8 mg, 0.09 mmol) is added and stirring is continued for about 2 h. The reaction mixture is poured into Et₂O, washed with H₂O (3x), saturated NH₄Cl (1x), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue is redissolved THF (3 mL); TBAF (0.1 mL, 1.0 M solution in THF) is then added and
- 25 this is stirred for about 1 h at 45°C. The mixture is concentrated *in vacuo* and the residue is then taken up in DMSO (2 mL). Aqueous NaOH (1 M, 1 mL) is added and the solution is stirred at RT for about 1 h. AcOH is added and purification by preparative HPLC, followed by lyophilization affords compound **1105**.

EXAMPLE 29A**Preparation of compound 1109****Step 1:**

- 5 Compound **29a1** is generated through the reaction of compounds **5a7** and **24a2** using the procedure of Step 3, Example 8A.

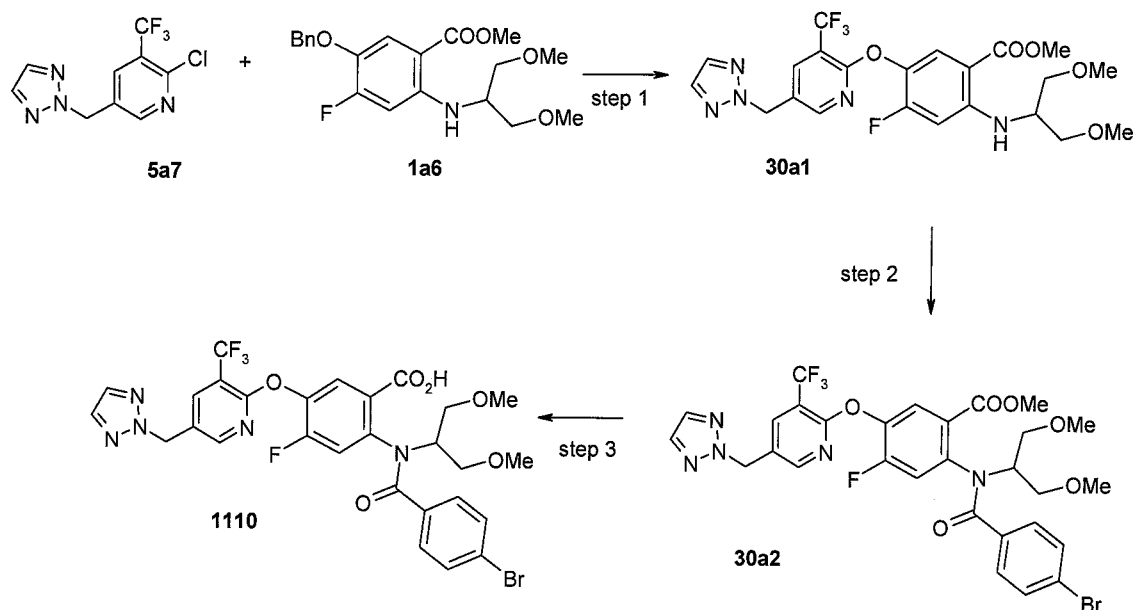
Step 2:

- Compound **29a1** is transformed to compound **29a2** using the procedure of Step 2, Example 22A.
- 10

Step 3:

Compound **29a2** is transformed to compound **1109** using the procedure of Step 3, Example 22A.

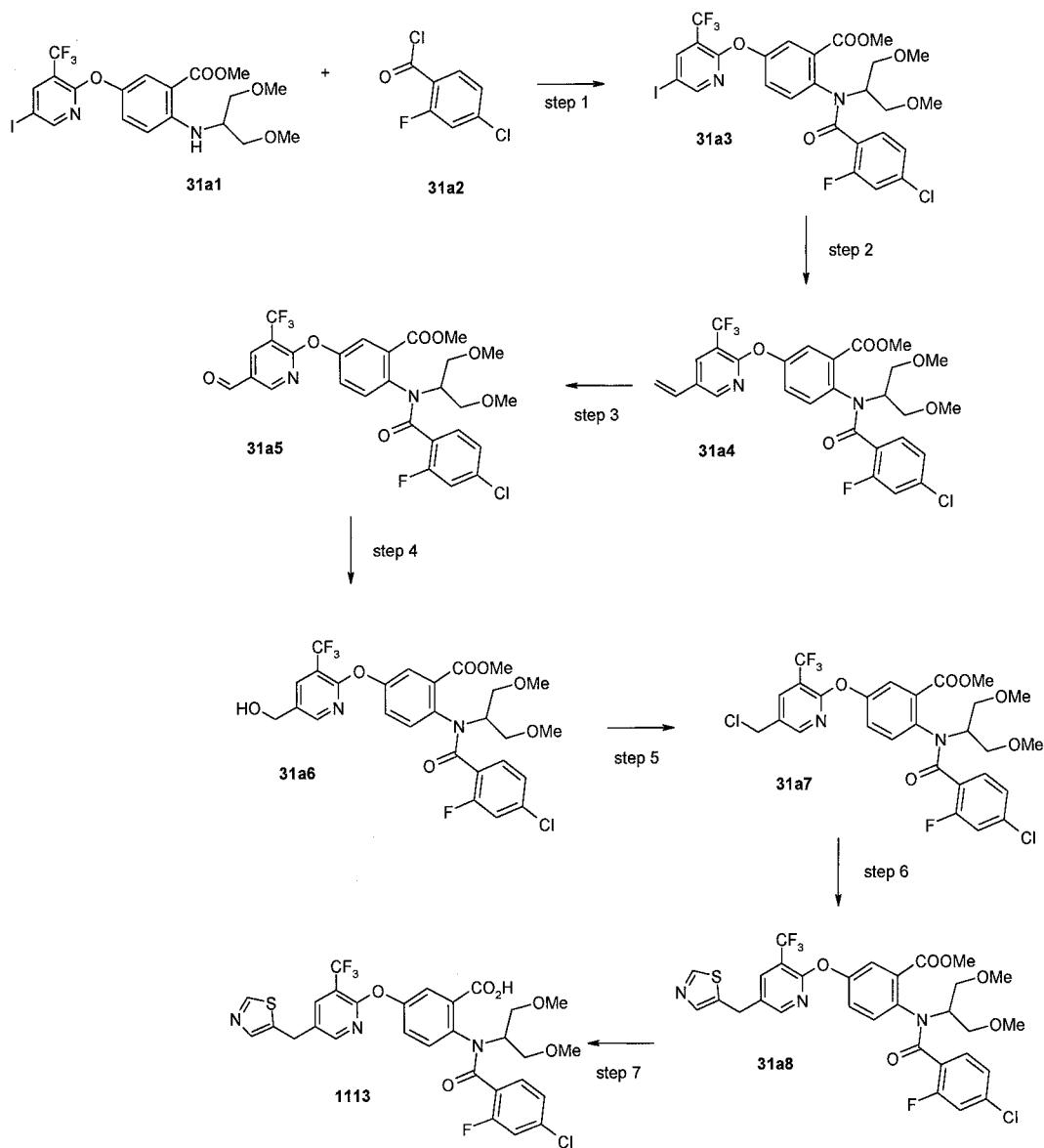
15

EXAMPLE 30A**Preparation of compound 1110****5 Steps 1 and 2:**

Compounds **5a7** and **1a6** are transformed to compound **30a1** is generated using the procedure of Steps 2 and 3, Example 8A and thereafter to compound **30a2** using the procedure of Step 2, Example 22A. ...

10 Step 3:

Compound **30a2** is transformed to compound **1110** using the procedure of Step 3, Example 22A.

EXAMPLE 31A**Preparation of compound 1113****5 Step 1:**

Using the procedure of Step 2, Example 22A, compound **31a1** (generated according to the condensation of **5a3** and **24a2** using the procedure described in Step 3, Example 24) is acylated with **31a2** (synthesized according to the procedure described in Step 6, Example 1A) to afford compound **31a3**.

10

Step 2:

Compound **31a3** is transformed to compound **31a4** using the procedure of Step 2,

Example 25A.

Steps 3 and 4:

Compounds **31a4** is transformed to **31a5** and thereafter to compound **31a6** using
5 the procedure of Steps 2 and 3, Example 5B, respectively.

Step 5:

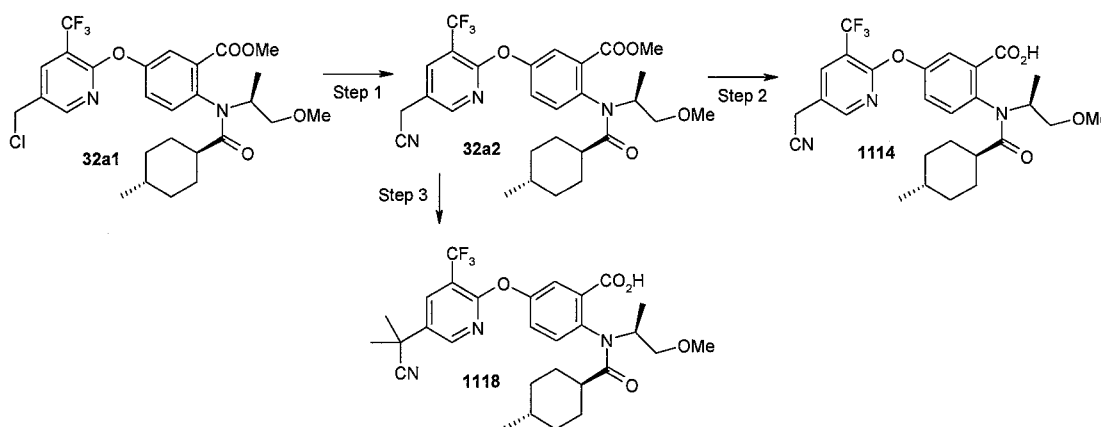
Compound **31a6** is transformed to compound **31a7** using the procedure of Step 3
Example 9A, respectively.

10

Steps 6 and 7:

To a solution of the chloride **31a7** (56 mg, 0.09 mmol) in DMF (1 mL) is added
Pd(PPh₃)₄ (9.9 mg, 0.009 mmol) and 5-(tri-butylstannyl)thiazole (64 mg, 0.17 mmol)
at RT. This solution is stirred at 120°C for about 12 min. MeOH (1 mL) and aqueous
15 NaOH (1 M, 1 mL) are added and stirring continues for about 3 h at RT. The reaction
mixture is concentrated, diluted in AcOH (4 mL) and purified by preparative HPLC.
The fractions are combined and solvent is removed by lyophilization to yield
compound **1113**.

20

EXAMPLE 32A**Preparation of compounds 1114 and 1118**25 Step 1:

The chloride **32a1** (356 mg, 0.639 mmol), which is prepared from phenol **10a2** using
the procedure described in Steps 1 to 3, Example 9A, is dissolved in DMSO (1 mL)

and NaCN (63 mg, 1.28 mmol) is added. The reaction is stirred at RT for about 1 h, then water is added. The mixture is extracted with DCM (3x), the organics are dried and concentrated. Purification by flash chromatography (1% to 5% MeOH in DCM) affords nitrile **32a2**.

5

Step 2:

The nitrile **32a2** (42 mg, 0.08 mmol) is dissolved in a THF (1 mL)/MeOH (0.5 mL)/H₂O (0.5 mL) mixture and an aqueous NaOH solution (10 N, 77 μ L, 0.77 mmol) is added. When the reaction is complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate compound **1114**.

10

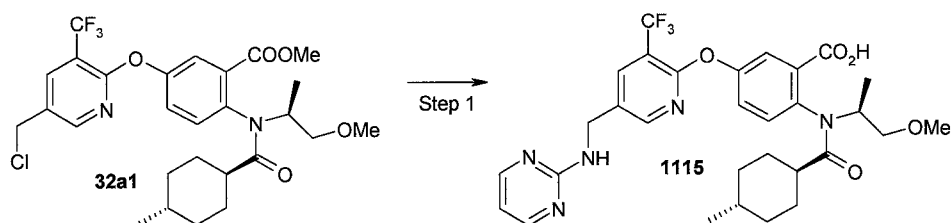
Step 3:

The nitrile **32a2** (49 mg, 0.09 mmol) and iodomethane (22 mL, 0.36 mmol) are dissolved in DMF (1 mL) at 0°C and a suspension of NaH (95% w/w, 4.5 mg, 0.18 mmol) in DMF (0.5 mL) is slowly added. After about 2 h, the reaction is neutralized with water, extracted with DCM (3x) and the organics are concentrated. The crude residue is re-dissolved in a THF (1 mL)/MeOH (0.5 mL)/H₂O (0.5 mL) mixture and an aqueous NaOH solution (10 N, 90 μ L, 0.90 mmol) is added. When the reaction is complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate compound **1118**.

20

EXAMPLE 33A

Preparation of compound 1115



25

Step 1:

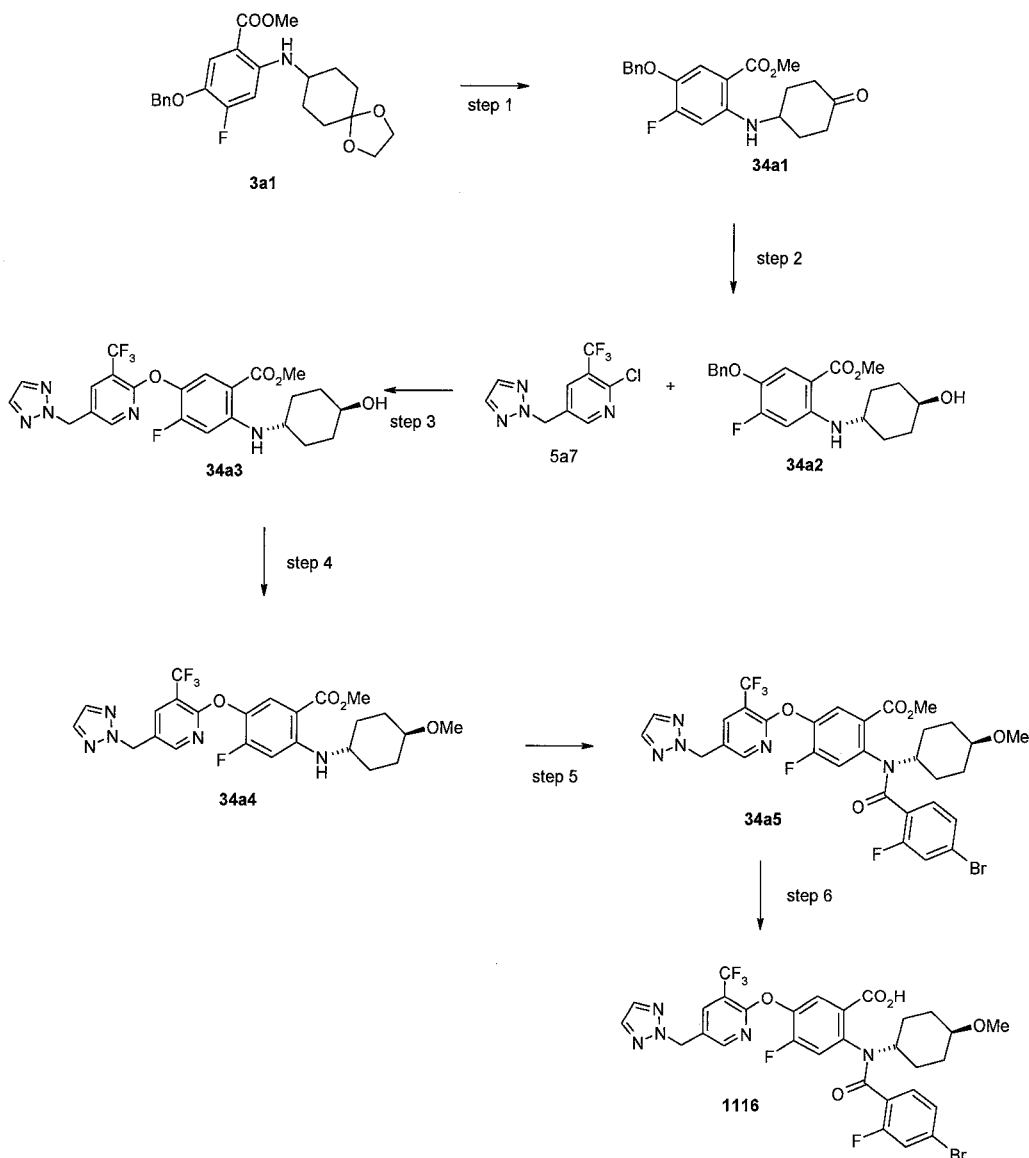
To a solution of chloride **32a1** (75 mg, 0.14 mmol) in DMF (1.5 mL) is added 2-amino pyrimidine (43 mg, 0.46 mmol) and a catalytic amount of KI (11 mg, 0.07 mmol). The mixture is warmed at 80°C for about 2 h, then cooled to RT. Acetonitrile (1 mL) and an aqueous solution of NaOH (2.5 N, 240 μ L, 0.6 mmol) are added, the mixture is

30

warmed at 50°C for about 2 h, then neutralized at RT with AcOH and injected onto the preparative HPLC to isolate compound **1115**.

EXAMPLE 34A

5 Preparation of compound 1116



Step 1:

To a solution of the ketal **3a1** (1.5g, 3.6 mmol) in toluene (7 mL) is added TFA (7 mL). This mixture is stirred for about 1 h, then water (0.4 mL) is added. The stirring is continued overnight and the mixture is concentrated. The resulting residue is diluted with EtOAc, washed with Na₂CO₃ (1 M), water and brine, dried with Na₂SO₄, filtered, evaporated and concentrated to obtain **34a1**.

Step 2:

The ketone **34a1** (1.7 g, 4.6 mmol) is suspended in MeOH (40 mL), and the solution is cooled to 0°C. NaBH₄ (87 mg, 2.3 mmol) is added and the mixture is stirred for about 1 h. The reaction is quenched with 1 M HCl, and the MeOH is evaporated under reduced pressure. The residue is diluted with EtOAc, and washed with aqueous, saturated NaHCO₃, water and brine. Then the residue is dried with Na₂SO₄, filtered, evaporated and employed in the subsequent reaction without further purification.

Step 3:

The benzyl ether **34a2** (410 mg, 1.1 mmol) is dissolved in MeOH (3 mL) and EtOAc (6 mL). 10% Pd/C (4 mg) is added and the flask is placed under an atmosphere of hydrogen. After about 2 h, the mixture is filtered on Celite®, and DMSO (9 mL) is added to the organic phase. The MeOH is removed under reduced pressure. Chloropyridine **5a7** (258 mg, 0.98 mmol) and cesium carbonate (448 mg, 1.4 mmol) are added, and the mixture is stirred at 70°C for about 4 h. The reaction mixture is then diluted with EtOAc, washed with aqueous, saturated NaHCO₃ and brine, dried with MgSO₄, filtered and evaporated. Purification by flash chromatography (10:90 to 50:50 EtOAc:Hex) yields **34a3**.

Step 4:

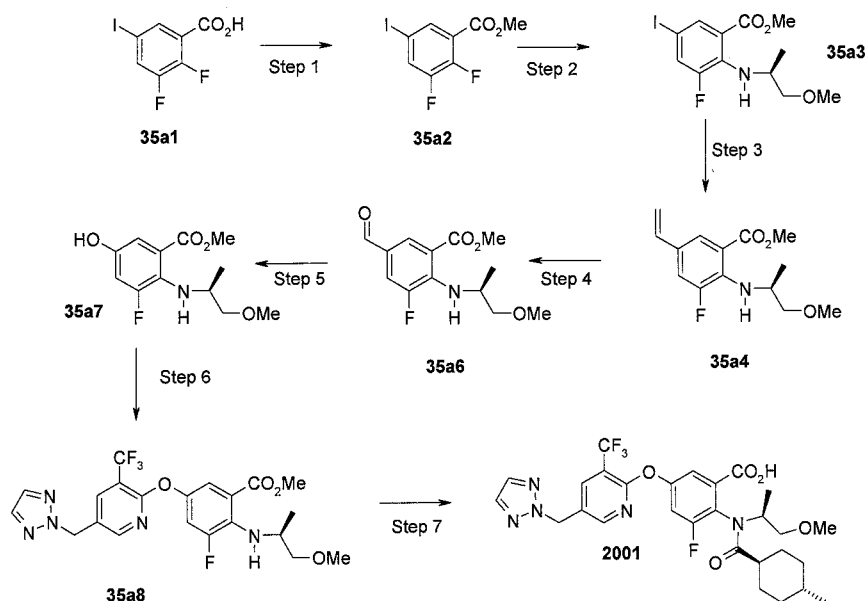
The alcohol **34a3** (400 mg, 1.1 mmol) is dissolved in DMF (10 mL) and iodomethane (1.7 mL, 27 mmol) is added. This solution is cooled to 0°C, then sodium hydride (133 mg, 3.3 mmol, 60 % in oil) is added and the mixture is stirred for about 4 h. Saturated NH₄Cl (10 mL) is added, followed by EtOAc (100 mL) and water (40 mL) are added and the mixture is shaken in a separatory funnel. The layers are separated and the organic layer is washed with brine, dried with MgSO₄, filtered, evaporated, concentrated and purified by flash chromatography (100% Hex to 60% Hex/EtOAc) to yield **34a4**.

Step 5:

Compound **34a4** is transformed to compound **34a5** using the procedure of Step 2, Example 22A.

Step 6:

Compound **34a5** is transformed to compound **1116** using the procedure of Step 3, Example 22A.

5 **EXAMPLE 35A****Preparation of compound 2001**Step 1:

Sulfuric acid (3 mL) is added to a solution of **35a1** (16.3 g, 57.4 mmol) in MeOH (200 mL). The solution is stirred overnight at 80°C. The mixture is cooled to RT, concentrated under reduced pressure, diluted with EtOAc (300 mL), washed with aqueous saturated sodium bicarbonate (3 x 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography (10% EtOAc in Hex) to afford methyl ester **35a2** as an oil which solidifies upon standing under high vacuum.

Step 2

(S)-(+)-1-methoxy-2-propylamine (1.90 g, 21.3 mmol) is added to a DMF (30 mL) solution of **35a2** (4.53 g, 15.2 mmol) and potassium carbonate (3.15 g, 22.8 mmol). The mixture is stirred at 75°C overnight, cooled to RT, diluted with saturated aqueous sodium bicarbonate (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with saturated aqueous sodium bicarbonate (2 x 100 mL), brine (100 mL) dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography (100% Hex

then 5% to 20% EtOAc in Hex) to afford **35a3** as an oil.

Step 3:

Pd(PPh₃)₄ (297 mg, 0.26 mmol) is added to a mixture of iodide **35a3** (2.36 g, 6.43 mmol) and tributylvinyl tin (2.06 mL, 7.07 mmol) in DMF (25 mL). The mixture is degassed by simultaneously bubbling Ar and sonicating the solution for about 15 min. The mixture is stirred at 90°C for about 30 min, cooled to RT, diluted with saturated aqueous sodium bicarbonate (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with saturated aqueous sodium bicarbonate (2 x 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by flash chromatography (100% Hex then 5% to 10% EtOAc in Hex) to afford **35a4** as an oil.

Step 4:

Vinyl compound **35a4** (1.45 g, 5.42 mmol) is dissolved in a mixture of acetone/*tert*-butanol/water (40 mL:10 mL:9.6 mL). The solution is cooled to 0°C, NMO (956 mg, 8.14 mmol) is added, followed by OsO₄ (2.5% in *tert*-butanol, 276 µL, 0.027 mmol). The solution is stirred at 0°C overnight, diluted with aqueous 10% sodium thiosulphate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with aqueous 10% thiosulphate (100 mL), brine (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude diol which is dissolved in THF (10 mL) and water (10 mL). This solution is cooled to 0°C, NaIO₄ is added (1.60 g, 7.47 mmol) and then stirred at 0°C for about 4 h. The reaction mixture is diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by flash chromatography (100% Hex then 5% to 20% EtOAc in Hex) to afford **35a6** as an oil.

Step 5:

Sulfuric acid (223 µL, 3.56 mmol) is added to a 0°C MeOH (20 mL) solution of **35a6** (640 mg, 2.38 mmol), followed by aqueous 30% hydrogen peroxide (404 µL, 3.57 mmol). The solution is stirred at 0°C for about 1 h then diluted with aqueous 10% KH₂PO₄ (50 mL) and extracted with ether (2 x 100 mL). The combined organic

phases are washed with aqueous 10% KH_2PO_4 (2 x 100 mL), brine (2 x 100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude phenol **35a7** is used directly in the next step without further purification.

5 Step 6:

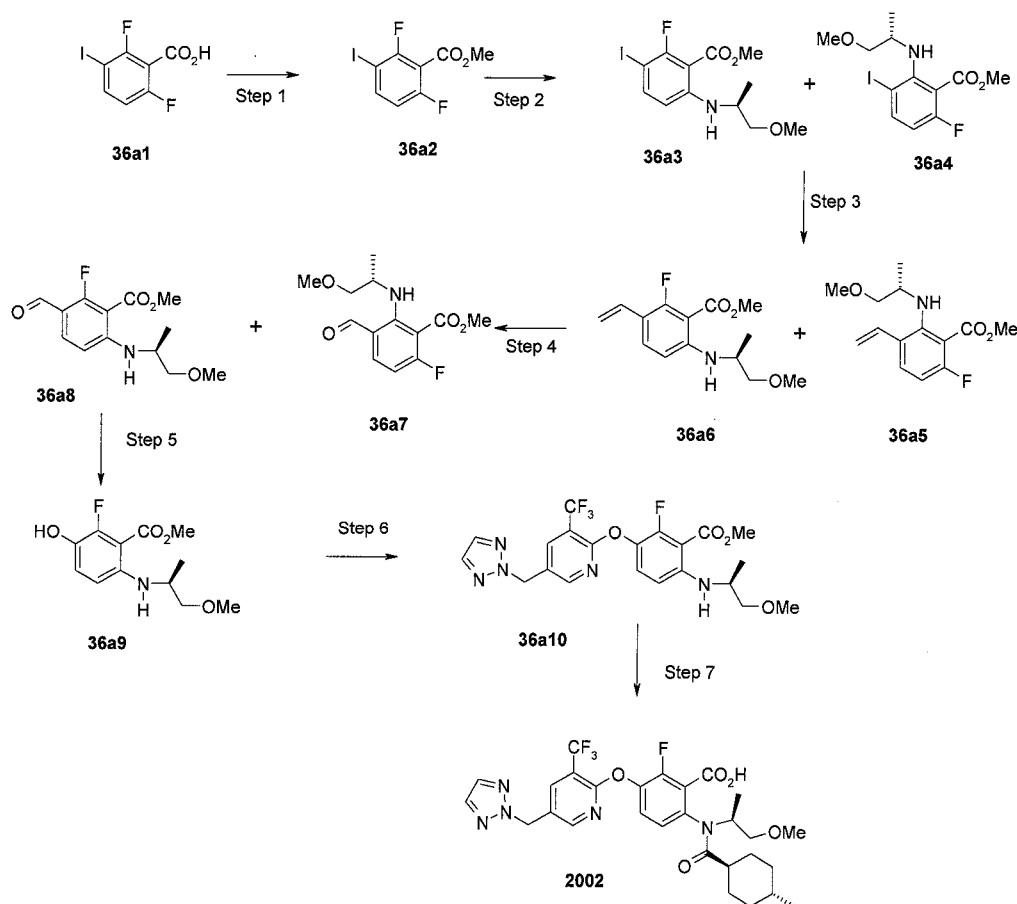
Compound **35a7** is transformed to compound **35a8** using the procedure of Step 1, Example 13A.

Step 7:

- 10 Compound **35a8** is transformed to compound **2001** using the procedure of Step 2, Example 13A.

EXAMPLE 36A

Preparation of compound 2002



15

Step 1:

Sulfuric acid (3 mL) is added to a solution of **36a1** (15.0 g, 36.9 mmol) in MeOH (200

mL) and the resulting solution is stirred overnight at 80°C. The mixture is cooled to RT, concentrated under reduced pressure, diluted with EtOAc (300 mL), washed with aqueous saturated sodium bicarbonate (3 x 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford methyl ester

5 **36a2**.

Step 2

(S)-(+)-1-methoxy-2-propylamine (1.49 g, 16.8 mmol) is added to a DMF (30 mL) solution of **36a2** (3.84 g, 12.9 mmol) and potassium carbonate (2.67 g, 19.3 mmol).

10 The mixture is stirred at 75°C overnight, cooled to RT, diluted with saturated aqueous sodium bicarbonate (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 100 mL), brine (100 mL) dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography (100% Hex
15 then 5% to 20% EtOAc in Hex) to afford a mixture of isomers **36a3** and **36a4**.

Step 3:

Pd(PPh₃)₄ (315 mg, 0.272 mmol) is added to a mixture of iodide **36a3** and **36a4** (2.00 g, 5.45 mmol) and tributylvinyltin (1.91 mL, 6.54 mmol) in DMF (40 mL). The
20 mixture is degassed by simultaneously bubbling Ar and by sonicating the solution for about 15 min. The mixture is stirred at 100°C for about 2.5 h, cooled to RT, diluted with aqueous saturated sodium bicarbonate (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and
25 concentrated under reduced pressure. The crude residue is purified by flash chromatography (100% Hexa then 5% to 10% EtOAc in Hex) to afford a mixture of compounds **36a5** and **36a6**.

Step 4:

30 Vinyl compounds **36a5** and **36a6** (1.19 g, 4.45 mmol) are dissolved in a mixture of acetone/*tert*-butanol/water (40 mL:10 mL:9.6 mL). The solution is cooled to 0°C, NMO (732 mg, 6.23 mmol) is added, followed by OsO₄ (2.5% in *tert*-butanol, 226 µL, 0.022 mmol). The solution is stirred at 0°C overnight, diluted with aqueous 10% sodium thiosulphate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined
35 organic phases are washed with aqueous 10% thiosulphate (100 mL), brine (2 x 100

mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude diols which are dissolved in THF (10 mL) and water (10 mL). This solution is cooled to 0°C and sodium metaperiodate is added (1.38 g, 6.45 mmol). The solution is stirred at 0°C for about 2 h. The reaction mixture is diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (100 mL), brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material is purified by flash chromatography (100% Hex then 5% to 10% EtOAc in Hex) to afford compounds **36a7** (elutes first) and **36a8** as an oil.

Step 5:

Sulfuric acid (147 μL , 2.35 mmol) is added to a 0°C MeOH (10 mL) solution of **36a8** (400 mg, 1.49 mmol), followed by aqueous 30% hydrogen peroxide (252 μL , 2.23 mmol). The solution is stirred at 0°C for about 1 h then diluted with aqueous 10% KH_2PO_4 (50 mL) and extracted with ether (2 x 100 mL). The combined organic phases are washed with aqueous 10% KH_2PO_4 (2 x 100 mL), brine (2 x 100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude phenol **36a9** is used directly in the next step without further purification.

Step 6:

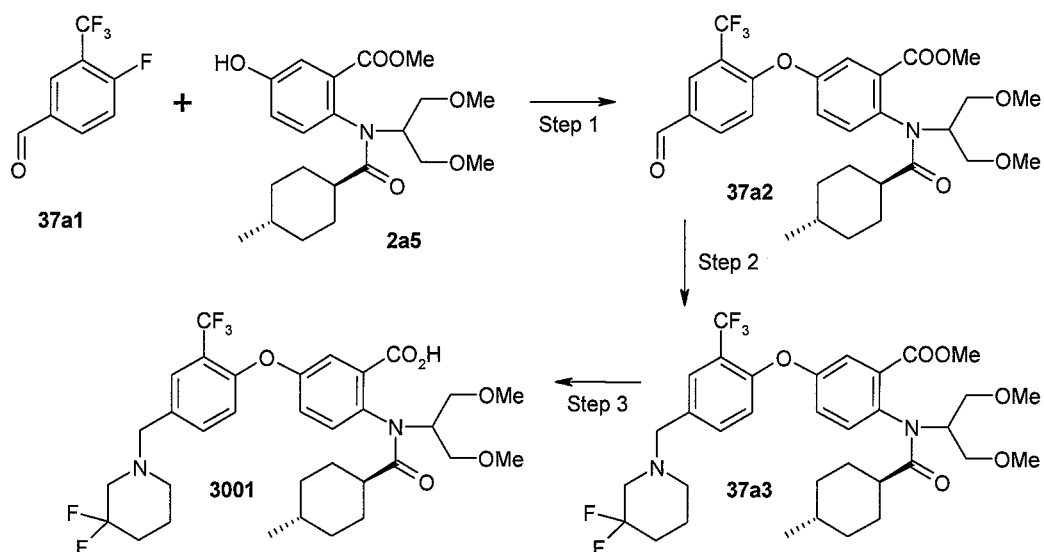
Compound **36a9** is transformed to compound **36a10** using the procedure described in Step 1, Example 13A.

Step 7:

Compound **36a10** is transformed to compound **2002** using the procedure described in Step 2, Example 13A.

EXAMPLE 37A

Preparation of compound 3001

**Step 1:**

Phenol **2a5** (1.0 g, 2.54 mmol) is combined with K_2CO_3 (878 mg, 6.35 mmol) and **37a1** (586 mg, 3.05 mmol) in DMSO (15 mL). The mixture is heated under Ar at 60°C until complete conversion, then cooled to RT. A saturated aqueous solution of $NaHCO_3$ is then added. The mixture is extracted with EtOAc (3x), the combined organics are dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude **37a2** which is used without further purification.

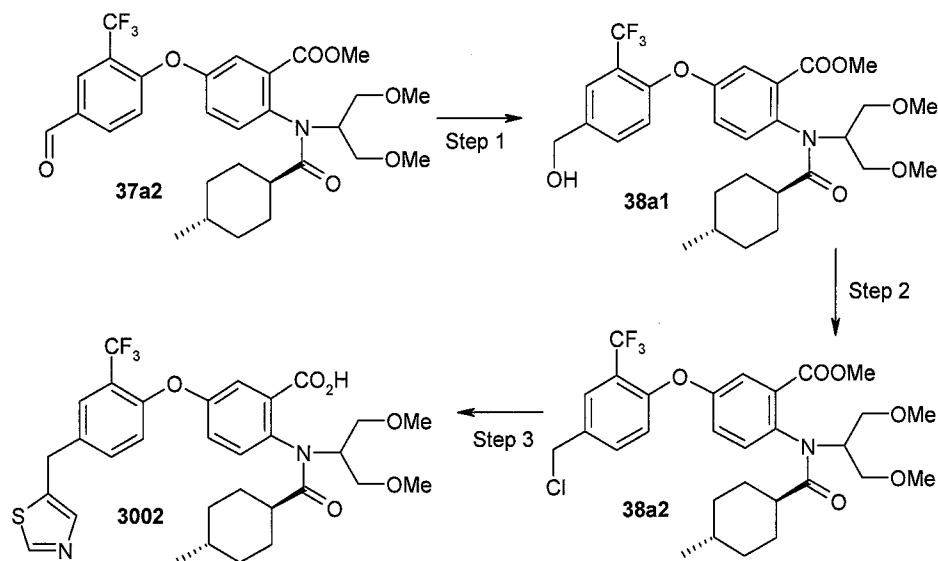
Step 2:

To a solution of **37a2** (100 mg, 0.18 mmol) and 3,3-difluoropiperidine hydrochloride (31 mg, 0.20 mmol) in DCE (1.5 mL) is added $NaBH(OAc)_3$ (52 mg, 0.25 mmol). The mixture is stirred at RT overnight, then water is added. The mixture is extracted with DCM (3x), the organics are dried and concentrated under reduced pressure. Purification by combiflash (15% EtOAc in hex) gives **37a3**.

Step 3:

Compound **37a3** is transformed to compound **3001** using the procedure of Step 2, Example 32A.

EXAMPLE 38A**Preparation of compound 3002**

**Step 1:**

The aldehyde **37a2** (1.30 g, 2.30 mmol) is dissolved in MeOH (25 mL) at 0°C and NaBH_4 (104 mg, 2.76 mmol) is added. After being stirred for about 1 h, the reaction is quenched with a saturated aqueous solution of citric acid and extracted with EtOAc (3x). The organics are dried over MgSO_4 , filtered and concentrated. Purification by combiflash gives alcohol **38a1**.

Step 2:

The alcohol **38a1** (700 mg, 1.23 mmol) is dissolved in DCM (15 mL) and thionyl chloride (0.19 mL, 2.59 mmol) and a catalytic amount of DMF (10 μL) is added. The reaction is stirred at RT; then successively washed with a saturated aqueous solution of citric acid, NaHCO_3 and brine. The organics are dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude chloride **38a2** is used as such without further purification.

Step 3:

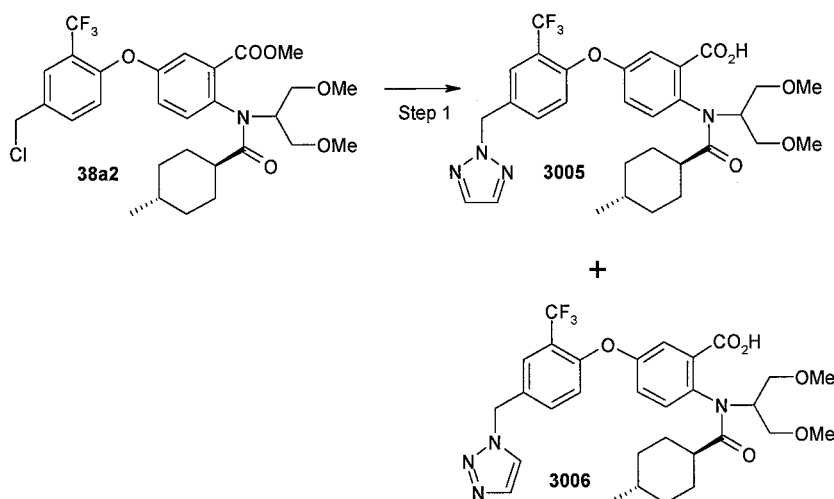
In a microwave tube, the chloride **38a2** (75 mg, 0.13 mmol) is put in degassed DMF (1 mL, degassed by bubbling a volume of Ar while sonicating for about 10 min) along with 5-(tributylstannyl)thiazole (96 mg, 0.26 mmol). $\text{Pd(PPh}_3)_4$ catalyst (15 mg, 13 μmol) is added and the tube is sealed and put in microwave at 125°C for 20 min. The mixture is diluted in EtOAc and washed with water (2x) and brine (2x). The combined organics are dried over MgSO_4 , filtered and concentrated. The crude residue is passed on a short silica gel column (20% to 70% EtOAc in hex) to remove most

impurities and the combined fractions are concentrated. The resulting yellow oil is re-dissolved in THF (1 mL)/MeOH (0.5 mL)/H₂O (0.5 mL) and NaOH (10 N, 0.13 mL, 1.3 mmol) is added. When complete, the reaction is neutralized with AcOH and injected onto a preparative HPLC to isolate **3002**.

5

EXAMPLE 39A

Preparation of compound 3005 and 3006

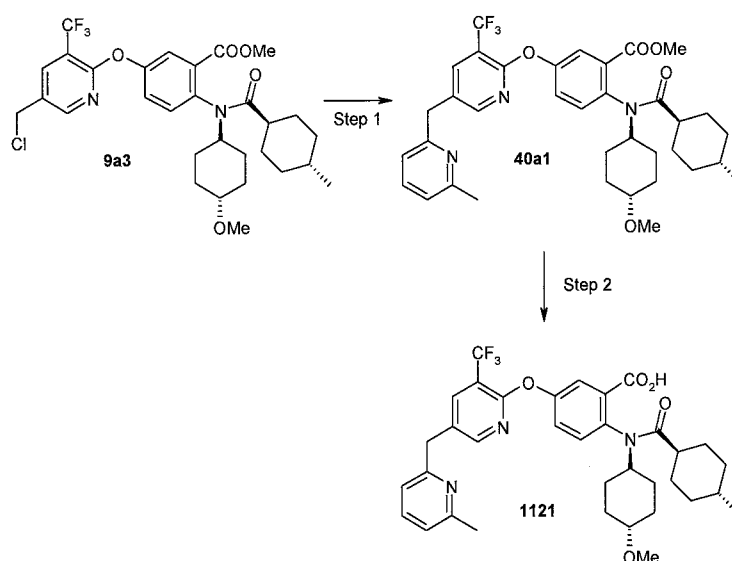


Step 1:

1,2,3-Triazole (15 μ L, 0.13 mmol) is added to a suspension of NaH (60% w/w, 10 mg, 0.26 mmol) in THF (0.5 mL) and stirred for about 15 min at RT. This mixture is transferred to a solution of chloride **38a2** (75 mg, 0.13 mmol) in dry DMF (1 mL) and is stirred overnight. The mixture is partially concentrated under reduced pressure and pre-adsorbed on silica gel for purification by combiflash (50% to 100% EtOAc in hex). Two products are recovered corresponding to each isomeric triazole intermediate. After being combined and concentrated, each intermediate is separately re-dissolved in THF (2 mL)/MeOH (1 mL) and NaOH (10 N, 0.13 mL, 1.3 mmol) is added. When complete, each reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate **3005** and **3006**.

20 EXAMPLE 40A

Preparation of compounds 1121

**Step 1:**

Compound **9a3** is transformed to compound **40a1** using the procedure of Step 1, Example 20A.

5

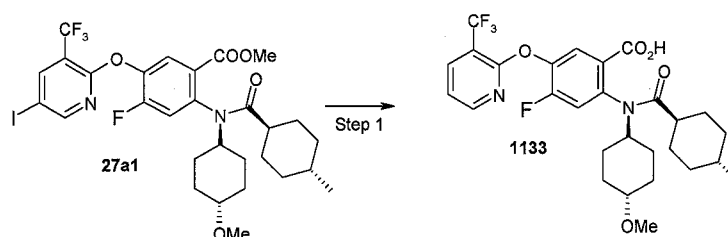
Step 2:

To the methyl ester **40a1** (27 mg, 41 μ mol) in MeOH and THF (1:1 mixture, 1 mL) is added an aqueous NaOH solution (1.0 M, 41 μ L, 41 μ mol). The mixture is stirred for about 2 days at RT, and then water is added. The aqueous layer is washed with Et₂O (2x) and lyophilized. The compound **1121** is quantitatively obtained in its sodium salt form.

10

EXAMPLE 41A**Preparation of compounds 1133**

15

**Step 1:**

The iodide **27a1** (72 mg, 0.104 mmol) is dissolved in MeOH (5 mL) and 10% Pd/C (50 mg) is added. The mixture is stirred for about 1 h under a balloon atmosphere of

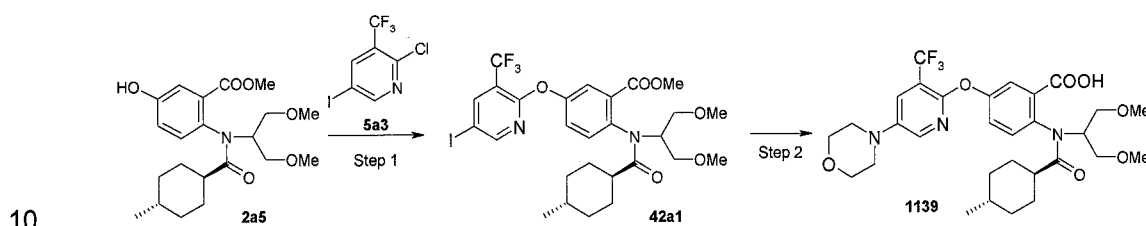
20

hydrogen. The mixture is filtered through Celite® and concentrated under reduced pressure. The crude residue is re-dissolved in DMSO (3 mL) and water (0.5 mL), then aqueous NaOH (10 N, 50 µL, 0.50 mmol) is added. When complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate

5 **1133**.

EXAMPLE 42A

Preparation of compounds 1139



Step 1:

Compound **42a1** is generated via the reaction of **2a5** (715 mg, 2.33 mmol) and pyridine **5a3** (879 mg, 2.23 mmol) using the procedure of Step 1, Example 16A.

15

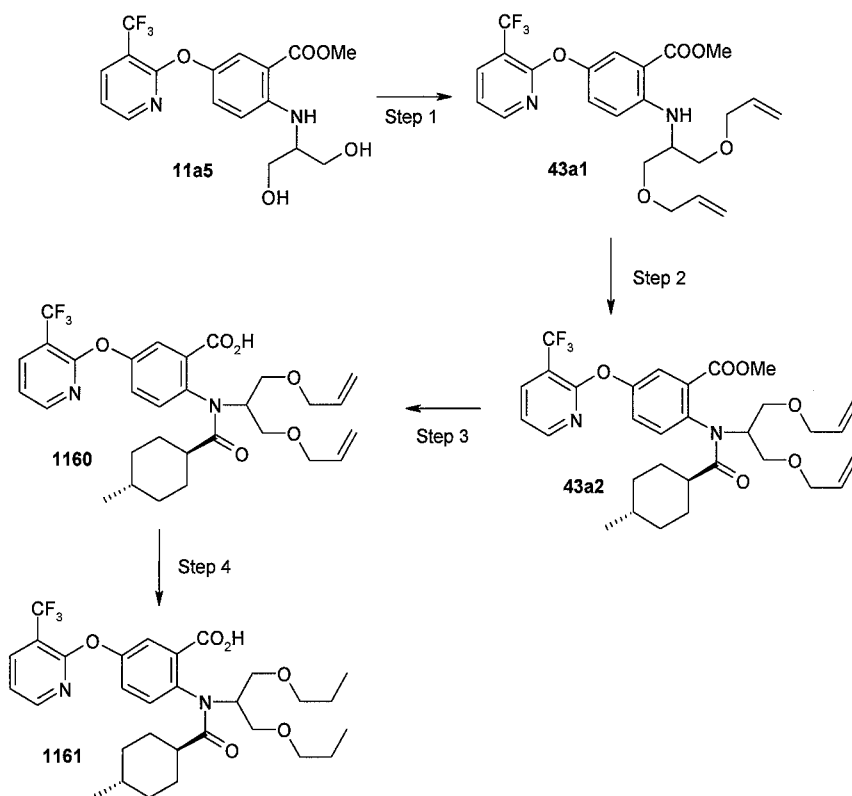
Step 2:

A mixture of iodide **42a1** (56.7 mg, 85 µmol), morpholine (42.5 mg, 0.49 mmol) and cesium carbonate (184 mg, 0.57 mmol) is prepared in anhydrous toluene (3 mL).

This mixture is sonicated and purged for about 10 min with a balloon atmosphere of Ar. To this mixture is added palladium acetate (1.9 mg, 9 µmol) and BINAP (8.0 mg, 13 µmol) and the heterogeneous mixture is further sonicated/purged for about 10 min upon which time it solubilizes. The reaction is placed at reflux for about 16 h, cooled to RT, then EtOAc is added and the mixture is washed with a saturated aqueous solution of NaHCO₃ (2x). The organics are dried over MgSO₄ and concentrated. The crude residue is re-dissolved in THF (1 mL)/MeOH (0.5 mL)/water (0.5 mL) and NaOH (10 N, 85 µL, 0.85 mmol) is added. When complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate **1139**.

20

25

EXAMPLE 43A**Preparation of compounds 1160 and 1161****5 Step 1:**

The diol **11a5** (221 mg, 0.57 mmol) is dissolved in DMF (3 mL) and cooled to 0°C. Allyl iodide (0.11 mL, 1.20 mmol) and sodium hydride (95%, 30.3 mg, 1.20 mmol) are successively added and the mixture is stirred at RT for about 1 h. Water is added and the mixture is extracted with DCM (3x). The organic phases are dried and concentrated. The crude residue is purified by combiflash (hex / EtOAc, 15% to 25%) to afford aniline **43a1**.

Step 2:

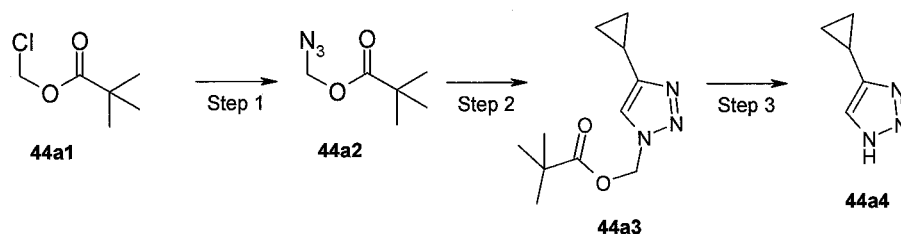
Compound **43a1** is transformed to compound **43a2** using the procedure of Step 2, Example 7A.

Step 3:

Compound **43a2** is transformed to compound **1160** using the procedure of Step 2, Example 32A.

Step 4:

Compound **1160** (18 mg, 31 μ mol) is dissolved in MeOH (3 mL) and activated Raney Nickel (50% slurry in water, 20 mg) is added. The reaction flask is purged and filled with a hydrogen atmosphere. After being stirred for about 1 h, the mixture is filtered through Celite® and rinsed thoroughly with MeOH. The filtrate is concentrated; the residue is re-dissolved in water/MeCN, filtered through a microdisc, then lyophilized to afford **1161**.

EXAMPLE 44A**10 Preparation of intermediate 44a4**

Reference: Loren, J.C.; Krasinski, A.; Fokin, V.V.; Sharpless, K.B. *Synlett* **2005**, 18, 2847.

Step 1:

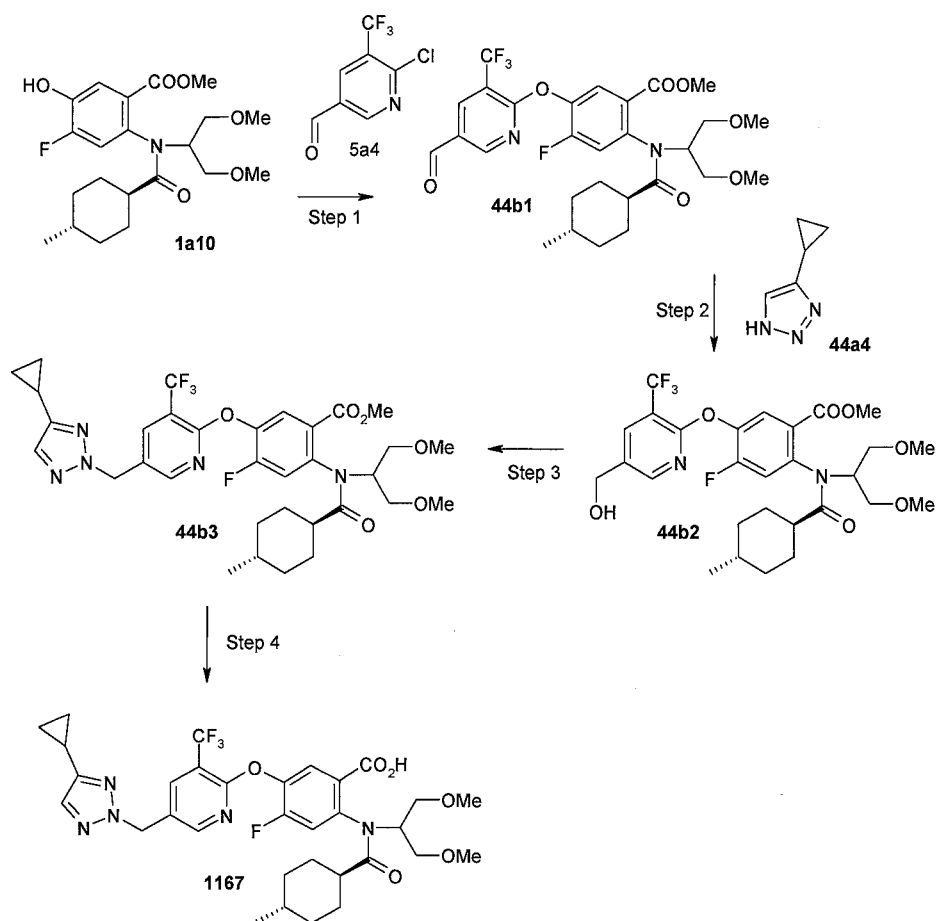
To a suspension of chloromethyl pivalate **44a1** (20 mL, 186 mmol) in water (37 mL) is added sodium azide (18.1 g, 279 mmol) and the mixture is warmed at 90°C for about 12 h. Additional water is then added and the phases are separated. The organic layer is passed through a filter funnel containing MgSO₄ to afford the azide **44a2**.

Step 2:

The azide **44a2** (100 mg, 0.64 mmol) and cyclopropylacetylene (54.7 mg, 0.83 mmol) are dissolved in *tert*-butanol (0.5 mL) and water (0.5 mL). An aqueous solution of copper sulfate (0.3 M, 0.43 mL, 0.13 mmol) is added followed by an aqueous solution of ascorbic acid sodium salt (1.0 M, 0.51 mL, 0.51 mmol). After stirring for about 16 h at RT, the mixture is diluted in EtOAc and water and the phases are separated. The organics are washed with a 5% aqueous NH₄OH/brine solution (2x), then dried over MgSO₄, and the solvent removed *in vacuo*. The oil corresponding to **44a3** is used as such for the next step.

Step 3:

To the ester **44a3** (102 mg, 0.46 mmol) in MeOH (1 mL) is added aqueous NaOH (1 N, 1 mL, 1 mmol). The reaction is stirred for about 30 min at RT, then neutralized with aqueous HCl (1 M, 1 mL, 1 mmol) and diluted in water. The mixture is extracted with EtOAc (3x), washed with brine, dried and the solvent is removed under reduced pressure. The crude oil corresponding to **44a4** is used as such.

EXAMPLE 44B**10 Preparation of compound 1167****Step 1:**

Compound **44b1** is generated via the reaction of **1a10** and chloropyridine **5a4** using the procedure of Step 1, Example 9A.

15 Step 2:

To the aldehyde **44b1** (1.25 g, 2.14 mmol) in MeOH (20 mL) chilled at 0°C is added NaBH₄ (98 mg, 2.6 mmol). When the reaction is complete, a saturated aqueous solution of citric acid is added. The mixture is extracted with EtOAc (3x), dried over MgSO₄, and concentrated. Purification by combiflash (hex / EtOAc, 15% to 50%)

5 affords **44b2**.

Step 3:

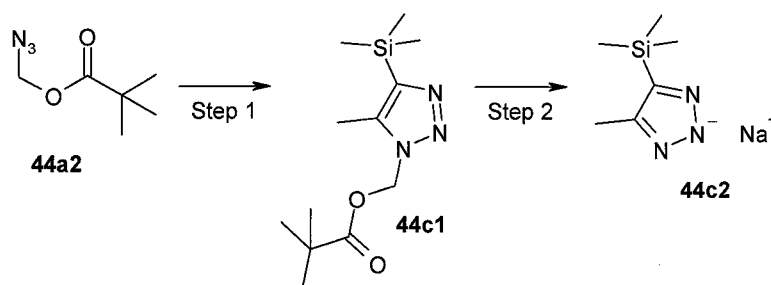
To a chilled (0°C) THF solution (2 mL) containing the alcohol **44b2** (100 mg, 0.17 mmol), PPh₃ (54 mg, 0.21 mmol) and triazole **44a4** (28 mg, 0.21 mmol) is slowly
10 added DEAD (38 µL, 0.21 mmol). The reaction is allowed to slowly warmed to RT over about 16 h. When the reaction is complete, the solvent is removed *in vacuo* and the crude residue is directly purified by combiflash (hex / EtOAc, 15% to 50%) to afford **44b3**.

15 Step 4:

The saponification using 1 eq of NaOH is performed using the procedure described in Step 2, Example 32A to give **1167** as the sodium salt.

EXAMPLE 44C

20 **Preparation of intermediate 44c2**



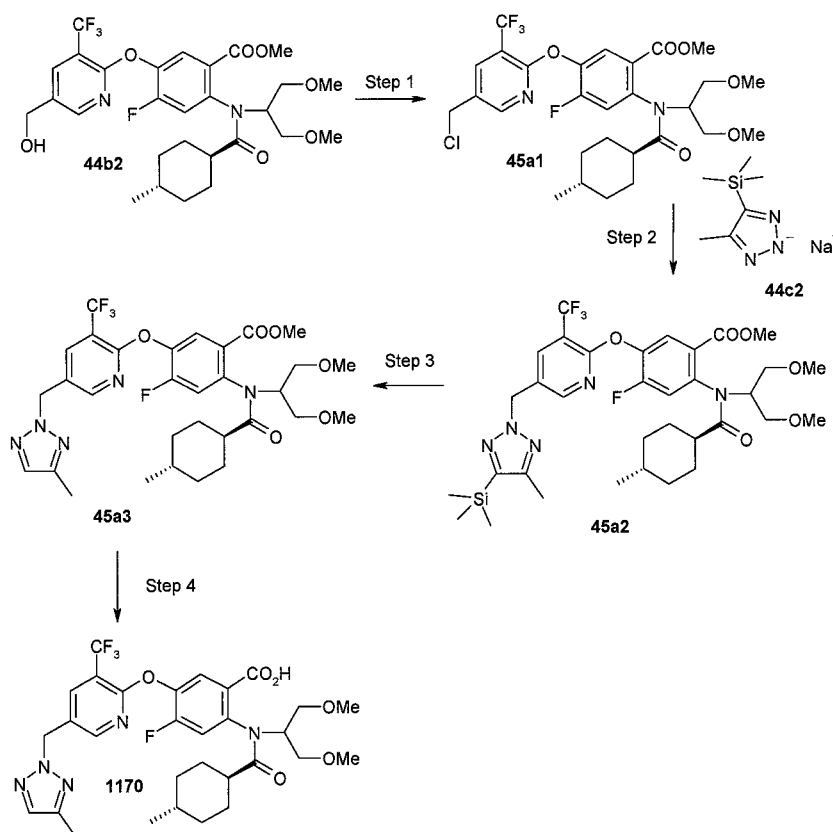
Step 1:

In a sealed tube, azide **44a2** (1.50 g, 9.54 mmol) is mixed with 1-(trimethylsilyl)-1-propyne (1.61 g, 14.32 mmol) in DCE (6 mL). The mixture is warmed at 80°C for
25 about 16h, then the solvent is concentrated *in vacuo* to afford triazole **44c1** which is directly used in the next step.

Step 2:

Triazole **44c1** (1.9 g, 7.05 mmol) is dissolved in MeOH (14 mL) and NaOH solution (10N, 1.55 mL, 15.5 mmol) is added. The reaction is stirred at RT for about 16 h. The solvent is concentrated under reduced pressure to afford the crude triazole **44c2** as the sodium salt.

5

EXAMPLE 45A**Preparation of compound 1170****Step 1:**

To the alcohol **44b2** (105 mg, 0.18 mmol) in DCM (2 mL) is added thionyl chloride (28 μ L, 0.38 mmol). To this solution is slowly added DMF (50 μ L) and the reaction proceeds at RT for about 1 h. A saturated aqueous solution of citric acid is then added and the layers are separated. The organics are successively washed with a saturated solution of NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated to afford chloride **45a1** which is used as such for the next step.

15

Step 2:

The chloride **45a1** (150 mg, 0.25 mmol) and **44c2** (53 mg, 0.30 mmol) are mixed in DMF (2 mL) and stirred at RT overnight. The mixture is diluted in EtOAc and washed with water (2x) and brine (1x), dried over MgSO_4 , filtered and concentrated.

Following purification by flash chromatography (hex / EtOAc, 15% to 40%), all

- 5 isomeric triazole intermediates are isolated in the same fraction. These isomers are further separated on a preparative HPLC. The less polar fraction corresponds to **45a2**.

Step 3:

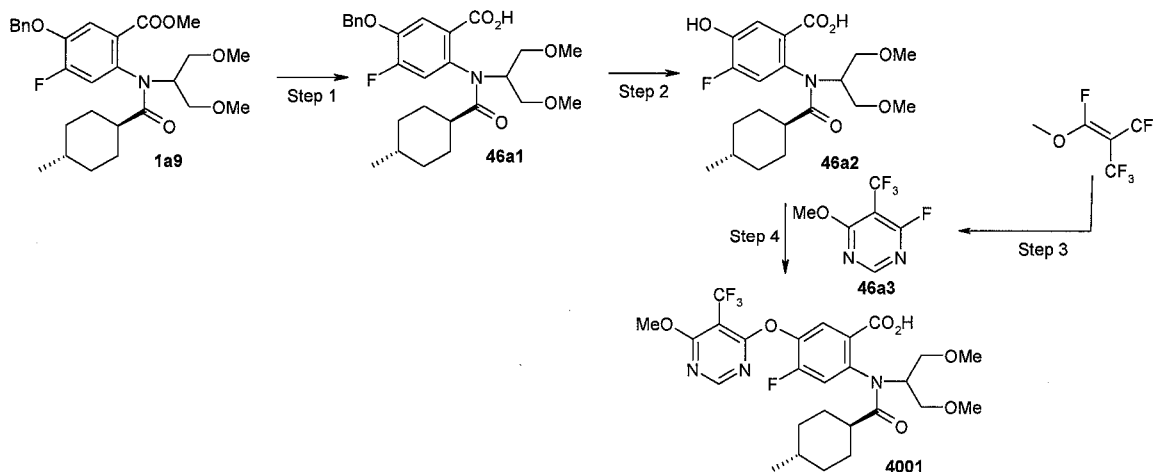
- 10 To the compound **45a2** (17 mg, 23 μmol) in THF (1 mL) is added TBAF (1.0 M in THF, 70 μL , 70 μmol). When the reaction is complete, the solvent is removed *in vacuo* and the crude residue containing **45a3** is used directly in the following step.

Step 4:

- 15 Compound **45a3** is transformed to compound **1170** using the procedure of Step 2, Example 32A.

EXAMPLE 46A

Preparation of compound 4001



- 20 Step 1:

To compound **1a9** (101 mg, 0.20 mmol) in THF (2 mL)/MeOH (1 mL)/water (1 mL) is added aqueous NaOH (10 N, 0.2 mL, 2.0 mmol) and the mixture is stirred at RT. When the reaction is complete, AcOH is added to neutralize the reaction and

solvents are removed under reduced pressure to afford crude **46a1** which is used directly in the next step.

Step 2:

- 5 The crude **46a1** (98 mg, 0.2 mmol) is dissolved in MeOH (3 mL)/EtOAc (5 mL) and activated Pd/C (10% w/w, 10 mg) is then added. The mixture is purged and filled with an atmosphere of hydrogen. When the reaction is complete, the mixture is filtered through a pad of Celite®, rinsed thoroughly with MeOH and the filtrate is concentrated. Acetonitrile and water are added and the mixture is lyophilized to
10 afford **46a2**.

Step 3:

- Formamidine acetate (15.3 g, 147 mmol) and 1,3,3,3-tetrafluoro-1-methoxy-2-(trifluoromethyl)prop-1-ene (20.8 g, 98 mmol) are mixed in DCM (100 mL) and water
15 (100 mL) at 0°C. To this vigorously stirred mixture is slowly added aqueous NaOH (6 N, 71 mL, 424 mmol) over about a 30 min period. Stirring is then continued for about 35 min. The layers are separated and the organic layer is concentrated. The crude residue is purified by bulb-to-bulb distillation (80°C, 3 mmHg) and purified further by Vigreux distillation under reduced pressure to afford **46a3**.

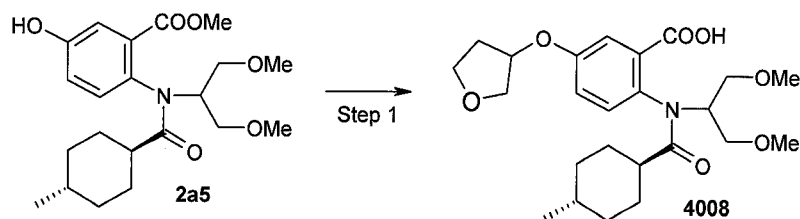
20

Step 4:

- Pyrimidine **46a3** (55 mg, 0.28 mmol) and phenol **46a2** (112 mg, 0.28 mmol) are mixed in DMSO (2 mL) along with K₂CO₃ (132 mg, 0.96 mmol). The mixture is stirred at RT for about 15 h, and then stirring is continued for about 1 h at 60°C. The mixture
25 is filtered to remove the solid residue. The filtrate is acidified with AcOH and injected onto the preparative HPLC to isolate **4001**.

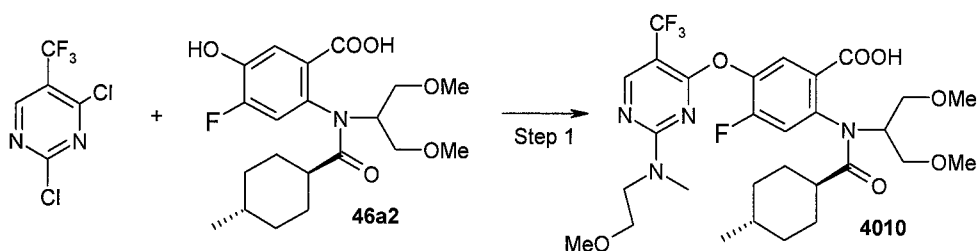
EXAMPLE 47A

Preparation of compound 4008



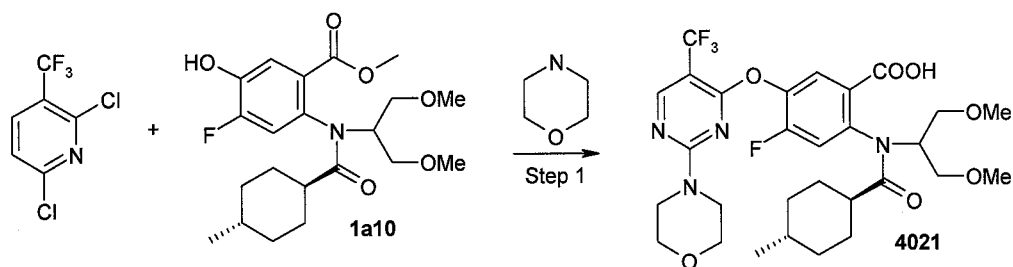
Step 1:

A mixture of phenol **2a5** (100 mg, 0.25 mmol), 3-hydroxytetrahydrofuran (31 mg, 0.36 mmol) and PPh₃ (100 mg, 0.38 mmol) are mixed in THF (2 mL) and cooled at 0°C. DIAD (70 µL, 0.38 mmol) is slowly added over about 10 min, and the reaction is stirred at RT. More reagent is added to complete conversion if necessary. Silica gel is then directly added and solvent is removed under reduced pressure. The crude product is quickly passed on a silica gel column eluting with a mixture of hex/EtOAc (20% to 70%) to remove most of the triphenylphosphine oxide. The combined fractions are combined and concentrated under reduced pressure. The residue is re-dissolved in THF (2 mL)/MeOH (1 mL) and NaOH (1N, 1 mL, 1 mmol) is then added. When complete, the reaction is neutralized with AcOH and injected onto the preparative HPLC to isolate **4008**.

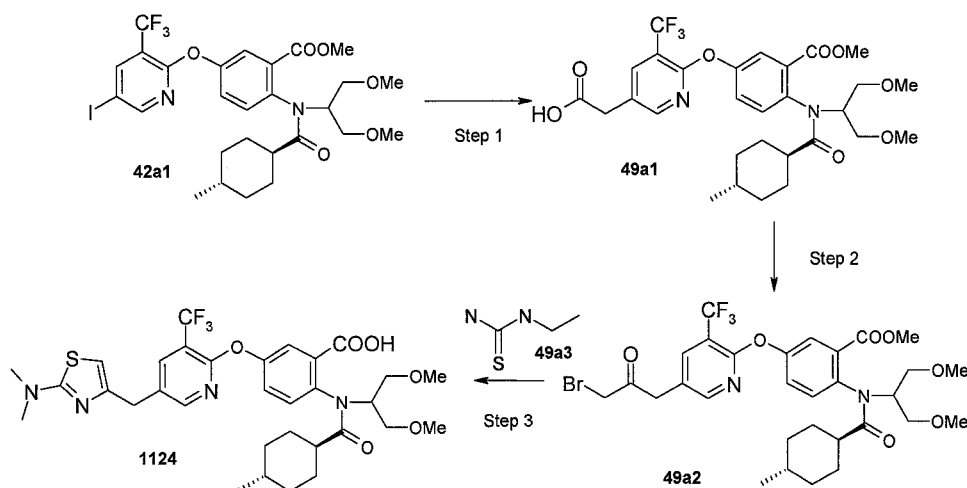
EXAMPLE 48A**Preparation of compound 4010**Step 1:

A suspension of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (50 mg, 0.22 mmol), *N*-(2-methoxyethyl)methylamine (20 mg, 0.22 mmol) and K₂CO₃ (90 mg, 0.65 mmol) is prepared in DMSO (2 mL) and stirred at RT. When the reaction is complete, phenol **46a2** (81 mg, 0.21 mmol) is added and the mixture is warmed at 65°C until the reaction is complete. When complete, the reaction is cooled and filtered through a microdisc to remove insoluble material, then the homogeneous solution is neutralized with AcOH and injected onto the preparative HPLC to isolate **4010**.

EXAMPLE 48B**Preparation of compound 4021**

**Step 1:**

A suspension of 2,6-dichloro-3-(trifluoromethyl)pyridine (75 mg, 0.35 mmol), morpholine (33 mg, 0.38 mmol) and K_2CO_3 (144 mg, 1.04 mmol) is prepared in DMSO (2 mL) and stirred at 60°C for about 6 h. When the reaction is complete, phenol **1a10** (30 mg, 0.073 mmol) is added and the mixture is warmed at 100°C for about 20 h. When complete, the reaction is diluted in water and the mixture is extracted with DCM (3x) and concentrated. The residue is then dissolved in THF (2 mL) / MeOH (1 mL) / water (1 mL) and NaOH solution (10N, 75 μ L, 0.75 mmol) is added. When complete, the mixture is filtered and the homogeneous solution is neutralized with AcOH and injected onto the preparative HPLC to isolate **4021**.

EXAMPLE 49A**Preparation of compound 1124****Step 1:**

Copper (I) iodide (28 mg, 0.147 mmol) is added to a dioxane (2 mL) solution of iodide **42a1** (195 mg, 0.286 mmol), dibenzyl malonate (207 μ L, 0.829 mmol), picolinic acid (35 mg, 0.286 mmol) and cesium carbonate (382 mg, 1.172 mmol). Argon is bubbled into the reaction mixture for about 2 min and the reaction vessel is

sealed and heated at 70°C for about 20 h. The reaction mixture is cooled to RT to receive more copper (I) iodide (28 mg, 0.147 mmol) and then resubmitted to 70°C for about 20 h. The mixture is cooled to RT, diluted with aqueous saturated ammonium chloride (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic
5 phases are washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is dissolved in EtOH (10 mL) to receive Pd/C (10% w/w, 80 mg). The reaction flask is evacuated and filled back with hydrogen at atmospheric pressure. The mixture is stirred at RT for about 4 h, filtered through Celite®, washed
10 with EtOH and heated to 80°C for about 1 h. The reaction mixture is concentrated under reduced pressure to afford crude **49a1** which is used directly in the next step.

Step 2:

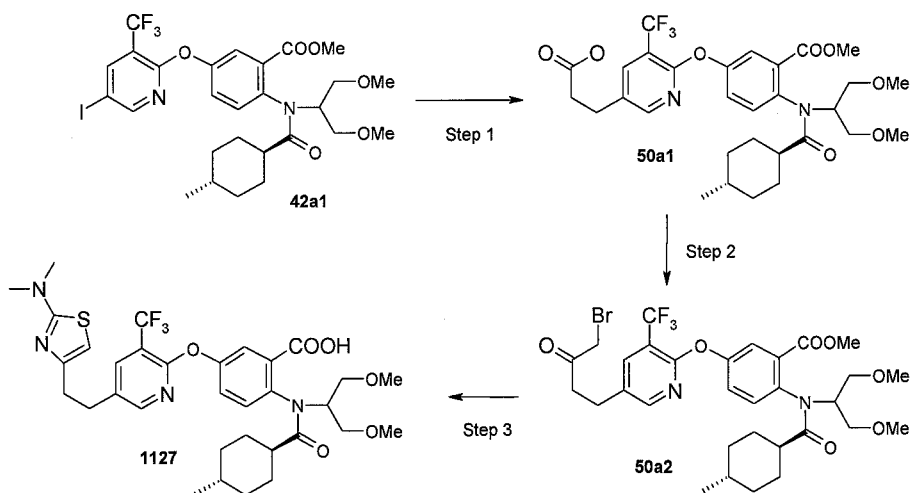
49a1 (214 mg, 0.35 mmol) is dissolved in DCM (8 mL), followed by the addition of
15 oxalyl chloride (0.3 mL, 0.2 M in DCM, 0.60 mmol) and DMF (0.01 mL). This mixture is stirred for about 1 h at 40°C, then concentrated *in vacuo*. The residue is redissolved in DCM (10 mL) and then CH₂N₂ (6.0 mL, 0.12 M in Et₂O, 0.72 mmol) is added dropwise. The solution is stirred for about 30 min and then concentrated *in vacuo*. The yellow oil is redissolved in THF (20 mL), cooled to 0°C and HBr (0.1 mL,
20 48%, 0.93 mmol) is added slowly. This is stirred for about 20 min. Saturated NaHCO₃ is slowly added and then the reaction is diluted with EtOAc, washed with H₂O (1x), NaHCO₃ (1x), brine (1x), dried over MgSO₄, filtered, concentrated *in vacuo* to yield yellow oil **49a2**.

25 Step 3:

The bromide **49a2** (80 mg, 0.12 mmol) is dissolved in *i*PrOH (3 mL) and the thiourea **49a3** (19 mg, 0.18 mmol) is added. The mixture heated at 70°C for about 4 h. The mixture is cooled to RT, then NaOH (0.2 mL, 0.25 M) is added and stirred for about 2 h. The mixture is diluted with AcOH and purified by preparative HPLC to yield the
30 desired compound **1124**.

EXAMPLE 50A

Preparation of compound 1127



Step 1: Compound **42a1** is transformed to compound **50a1** using the procedure of Step 3, Example 28A.

5

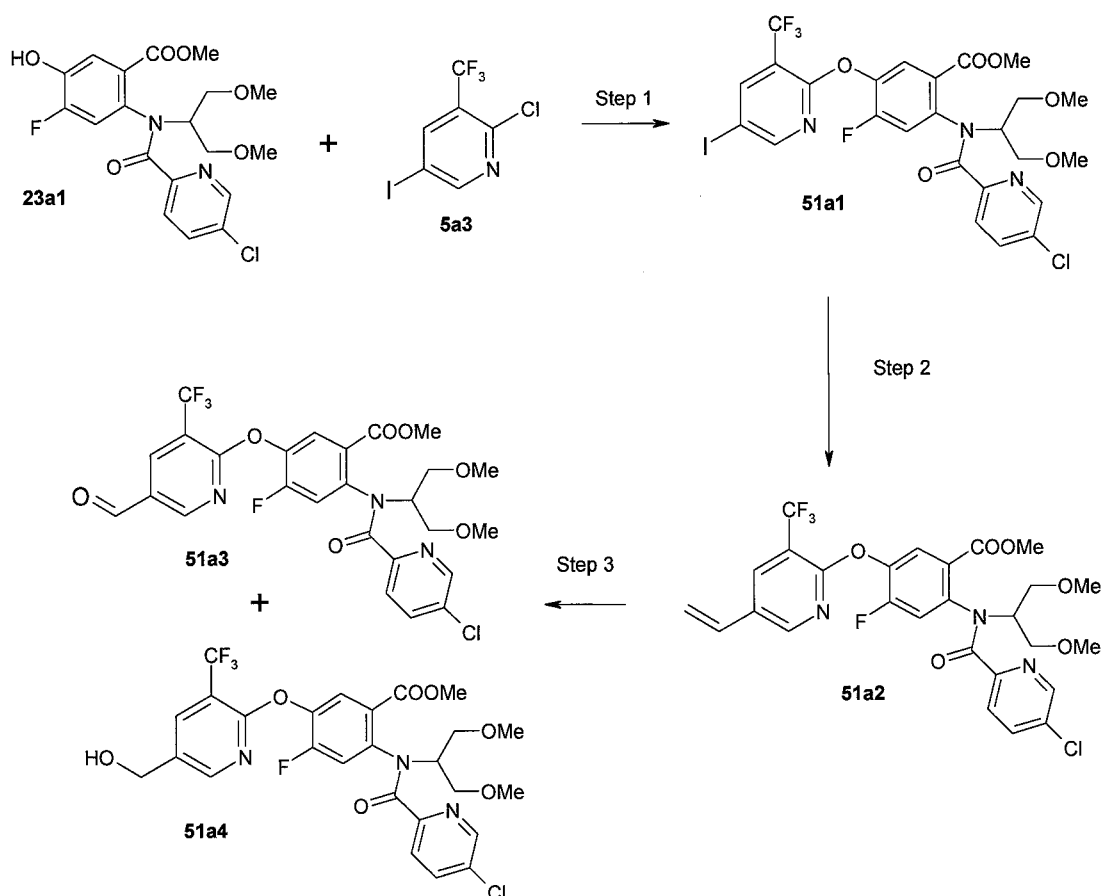
Step 2: Compound **50a1** is transformed to compound **50a2** using the procedure of Step 2, Example 49A.

Step 3: Compound **50a2** is transformed to compound **1127** using the procedure of Step 3, Example 49A.

10

EXAMPLE 51A

Preparation of intermediates **51a3** and **51a4**

**Step 1:**

To a solution of iodide **5a3** (191 mg, 0.62 mmol) in DMSO (3 mL) is added CsCO₃ (216 mg, 0.66 mmol) and **23a1** (189 mg, 0.44 mmol). This is stirred at 75°C for about
 5 4 h and then cooled to RT. The mixture is washed with water and brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. Purification by flash chromatography using (20:80 to 60:40) EtOAc/Hex affords an off-white solid **51a1**.

Step 2:

To a solution of **51a1** (256 mg, 0.37 mmol) in dioxane (3 mL) is added tributyl(vinyl)tin (0.14 mL, 0.48 mmol) at RT. The solution is degassed by bubbling a
 10 balloon of Ar into it. Dichloro-bis(triphenylphosphine)palladium (26 mg, 0.04 mmol) is added and the reaction mixture is heated at reflux for about 1.5 h. The mixture is concentrated and purified by flash chromatography using (10:90 to 70:30)
 15 EtOAc/Hex to obtain **51a2**.

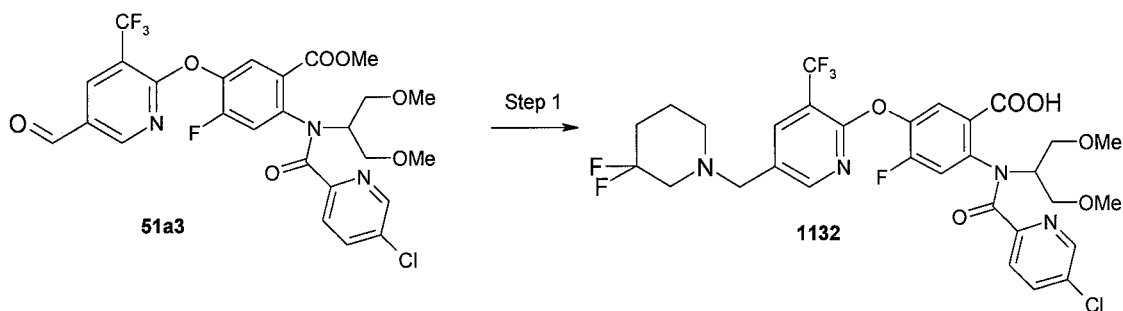
Step 3:

To a solution of **51a2** (181 mg, 0.30 mmol) in water (0.5 mL), acetone (2 mL) and

MeOH (0.4 mL) is added OsO₄ (0.04 mL, 2.5% solution in *t*-BuOH) and NMO (40 mg, 0.34 mmol) at RT. This is stirred at RT for about 1.5 h. Sodium periodate (71 mg, 0.33 mmol) is then added and reaction mixture is stirred at RT for about 16 h. The reaction mixture is poured into a saturated solution of aqueous Na₂S₂O₃ and then extracted with EtOAc (4x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. The residue is dissolved in MeOH (2 mL) and NaBH₄ (58 mg, 1.5 mmol) is slowly added and stirred for about 1 h at RT. The reaction mixture is poured into a saturated solution of aqueous NH₄Cl and then extracted with EtOAc (3x). The organic layers are combined, washed with brine, dried over anhydrous Na₂SO₄, filtered under vacuum and concentrated. Purification by flash chromatography using (30:70 to 80:20) EtOAc/Hex yields a mixture of aldehyde **51a3** and alcohol **51a4**.

EXAMPLE 51B

Preparation of compound 1132

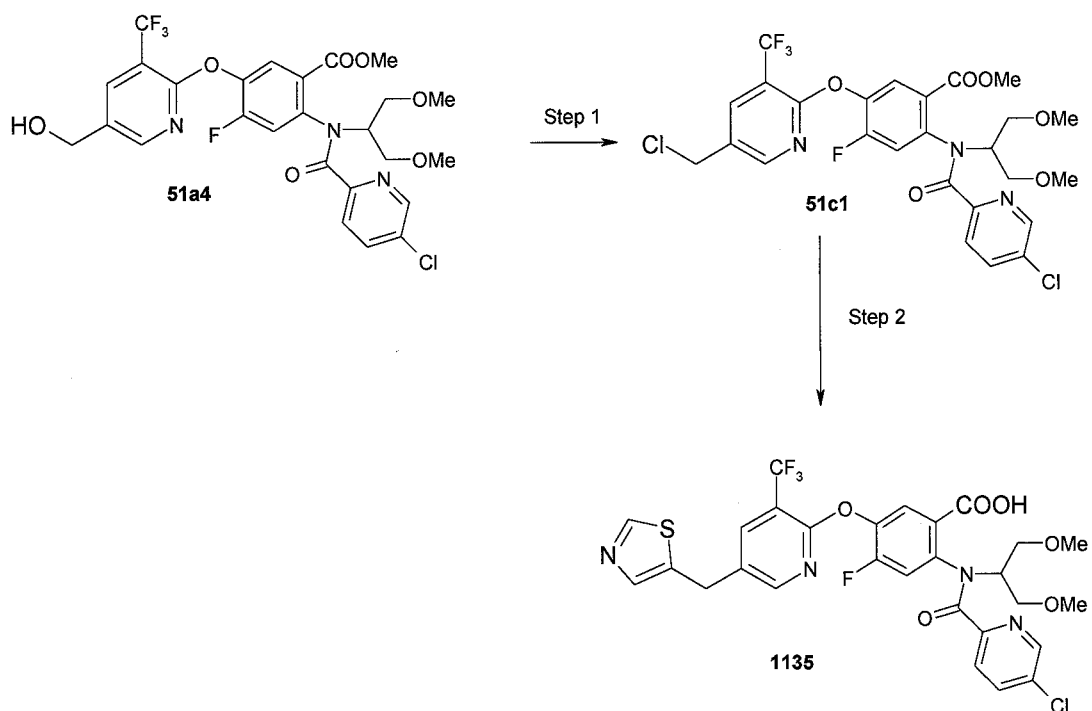


Step 1:

Compound **51a3** is transformed to compound **1132** using the procedure of Step 5, Example 5A.

EXAMPLE 51C

Preparation of compounds 1135

Step 1:

Compound **51a4** is transformed to compound **51c1** using the procedure of Step 2, Example 38A.

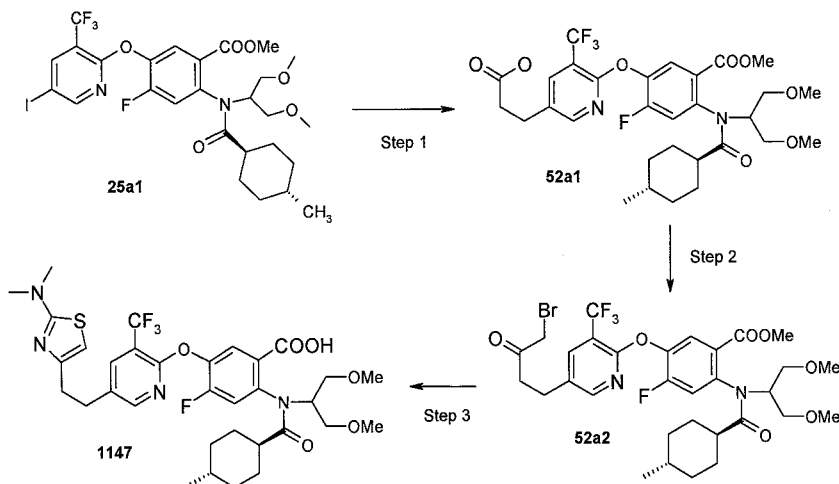
5

Step 2:

Compound **51c1** is transformed to compound **1135** using the procedure of Step 3, Example 38A.

10

EXAMPLE 52A**Preparation of compounds 1147**

**Step 1:**

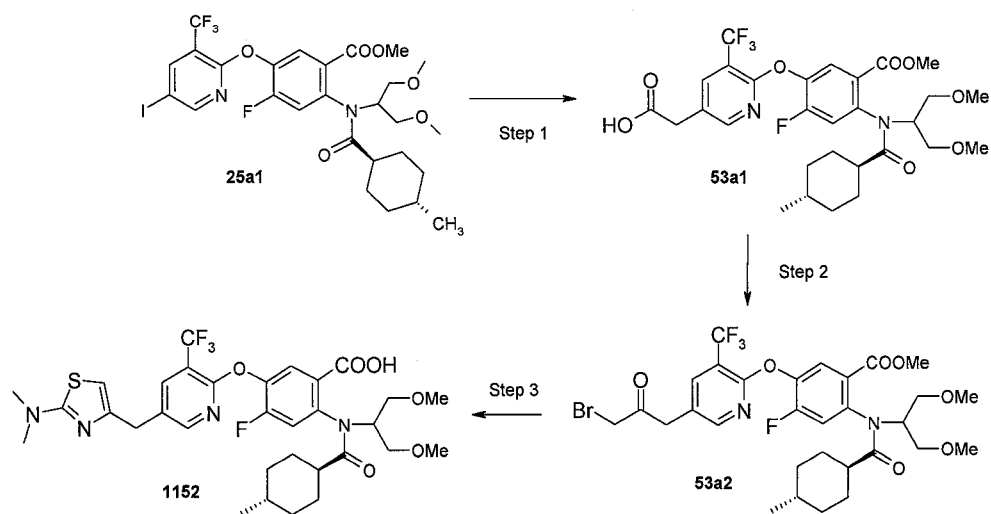
Compound **25a1** is transformed to compound **52a1** using the procedure of Step 3,
 5 Example 28A.

Step 2: Compound **52a1** is transformed to compound **52a2** using the procedure of
 Step 2, Example 49A.

10 **Step 3:** Compound **52a2** is transformed to compound **1147** using the procedure of
 Step 3, Example 49A.

EXAMPLE 53A**Preparation of compound 1152**

15



Step 1:

Compound **25a1** is transformed to compound **53a1** using the procedure of Step 1,
5 Example 49A.

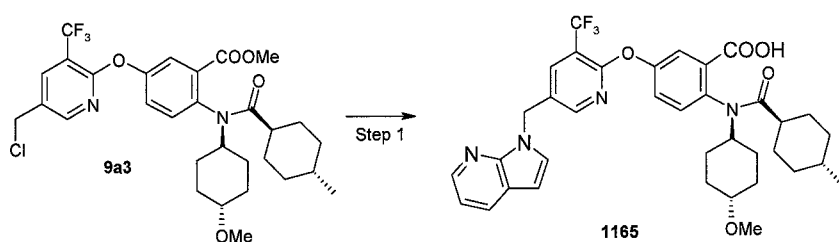
Step 2:

Compound **53a1** is transformed to compound **53a2** using the procedure of Step 2,
10 Example 49A.

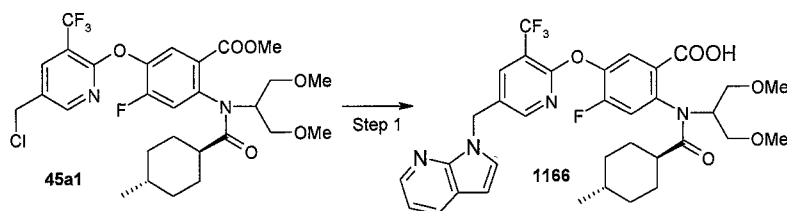
Step 3:

Compound **53a2** is transformed to compound **1152** using the procedure of Step 3,
Example 49A.

15 **EXAMPLE 54A**

Preparation of compounds 1165**Step 1:**

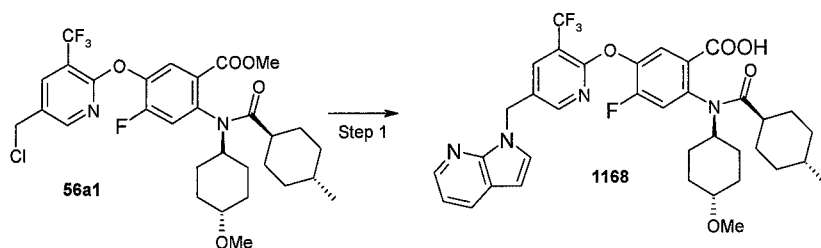
To the solution of 7-azaindole (15 mg, 0.13 mmol) dissolved in anhydrous DMF (1 mL), at RT is added cesium carbonate (55 mg, 0.17 mmol) followed by the addition of the benzylic chloride **9a3** (dissolved in anhydrous DMF 0.5 mL) is added, followed by KI (3.5 mg, 0.02 mmol). This is heated at 110°C for about 14 h, then cooled to RT.
25 THF (1 mL), MeOH (1 mL) and NaOH (1 M, 1 mL) is added and then this is stirred for about 24 h at RT. The mixture is then concentrated, diluted with AcOH and purified by preparative HPLC to yield the desired product **1165**.

EXAMPLE 55A**Preparation of compound 1166**

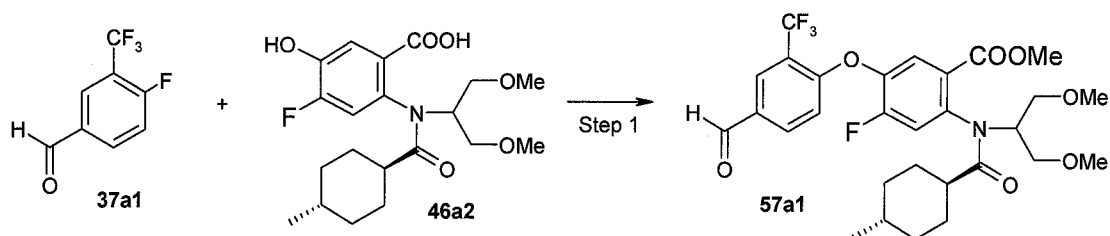
5

Step 1:

Compound **45a1** is transformed to compound **1166** using the procedure described in Step 1, Example 54A.

EXAMPLE 56A**Preparation of compounds 1168**Step 1:

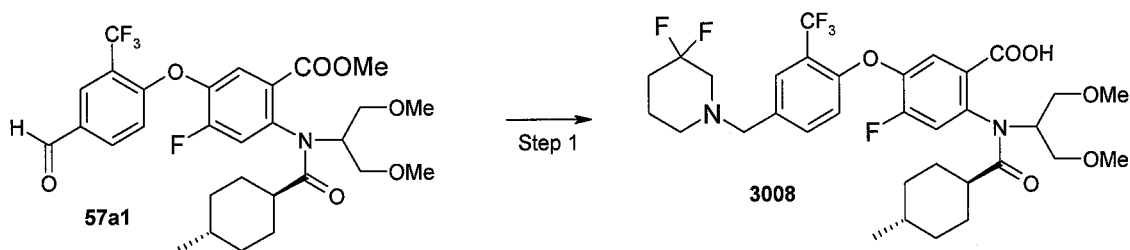
Compound **56a1** is transformed to compound **1168** using the procedure of Step 1, Example 55A.

EXAMPLE 57A**Preparation of intermediate 57a1**

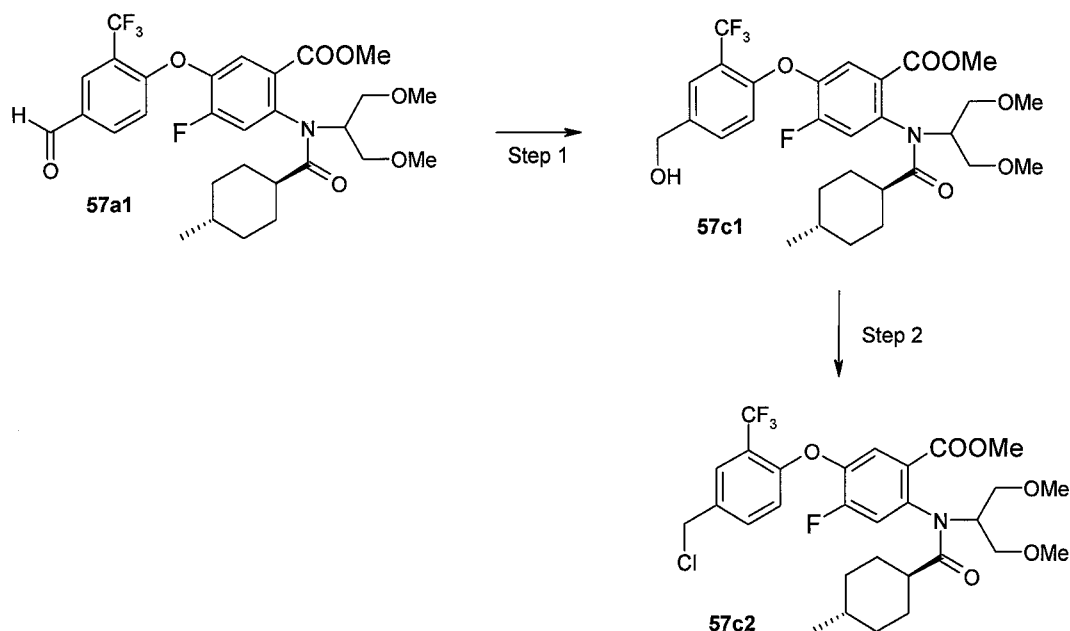
20

Step 1:

Compound **57a1** is generated via the reaction of compounds **37a1** and **46a2** using the procedure of Step 1, Example 37A.

EXAMPLE 57B**5 Preparation of compound 3008****Step 1:**

Compound **57a1** is transformed to compound **3008** using the procedure of Step 5, Example 5A.

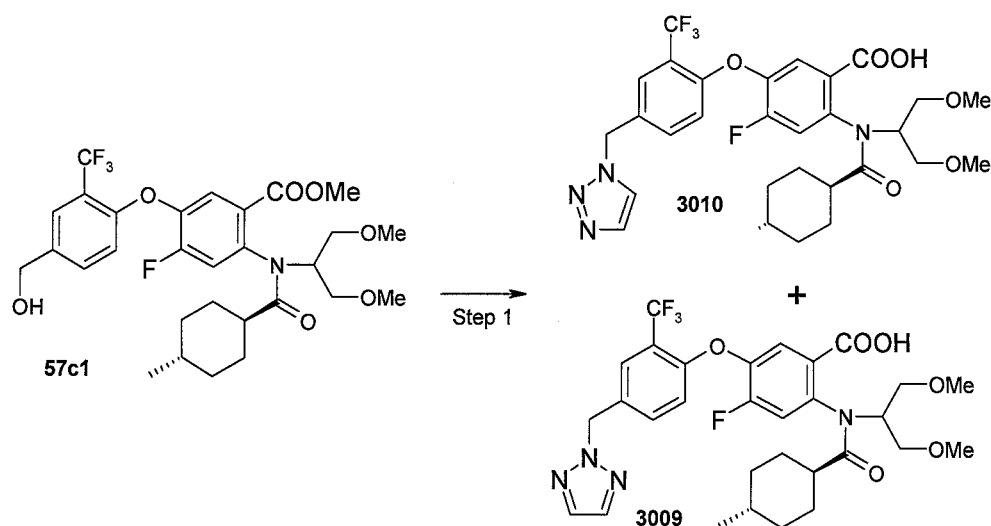
EXAMPLE 57C**Preparation of intermediate 57c2**

Step 1:

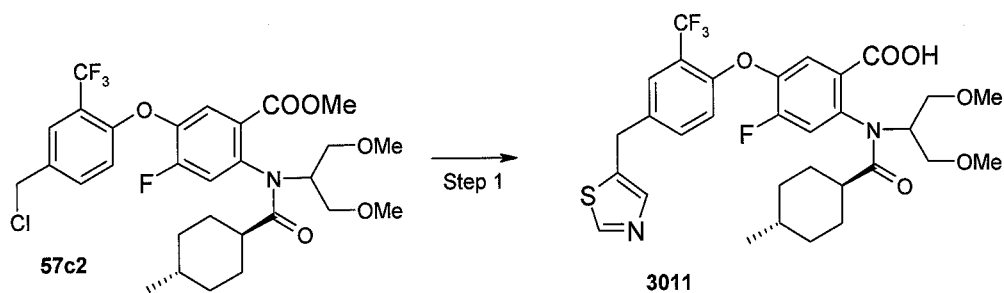
Compound **57a1** is transformed to compound **57c1** using the procedure of Step 2, Example 9A.

5 Step 2:

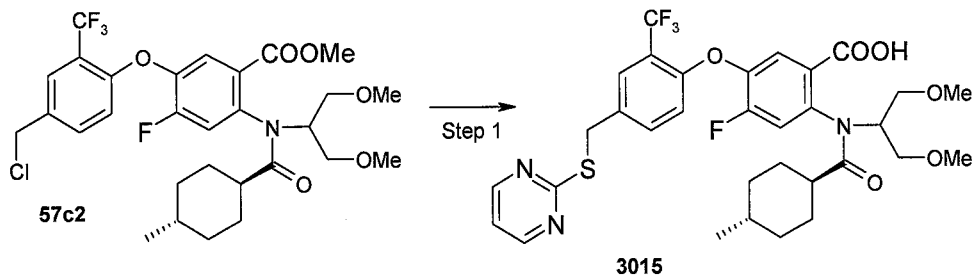
Compound **57c1** is transformed to compound **57c2** using the procedure of Step 3, Example 9A.

EXAMPLE 57D10 **PREPARATION OF COMPOUNDS 3009 AND 3010**Step 1:

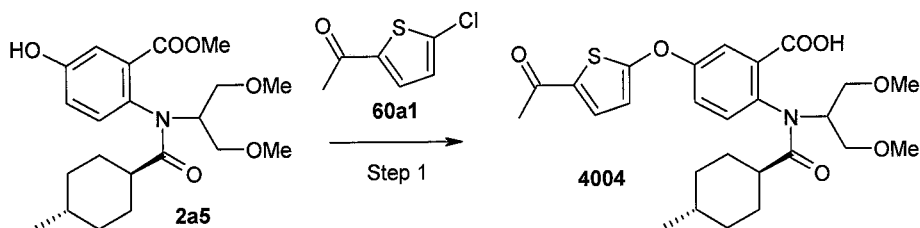
To a solution of **57c1** (49 mg, 0.08 mmol) in THF (1 mL) is added PPh_3 (24 mg, 0.09 mmol) and triazole (0.005 mL, 0.08 mmol). The solution is cooled to 0 °C and DEAD (0.017 mL, 0.09 mmol) is added. This is stirred at 0°C for about 45 min, warmed to RT and stirring is continued for about another 72 h. MeOH (1 mL) and NaOH (1mL, 1 M solution in water) are added and this mixture is stirred for about 24 h at RT. The reaction mixture is then concentrated, dissolved in AcOH/MeOH (4 mL, 1:1) and purified by preparative HPLC. The fractions are combined and solvent removed by lyophilization to yield **3010** and **3009**.

EXAMPLE 58A**Preparation of compound 3011**5 Step 1:

Compound **57c2** is transformed to compound **3011** using the procedure of Step 3, Example 38A.

EXAMPLE 59A10 **Preparation of compound 3015**Step 1:

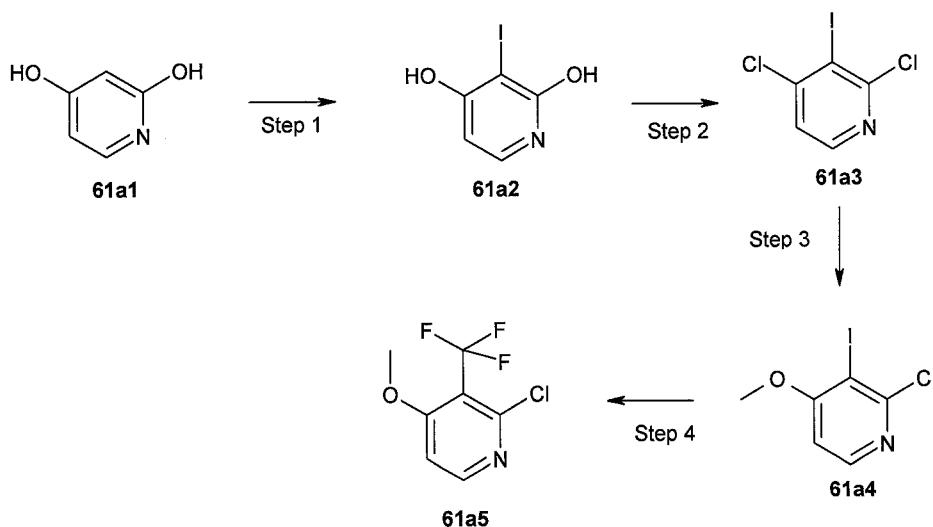
Compound **57c2** is transformed to compound **3015** using 2-mercaptopyrimidine in the procedure of Step 1, Example 33A.

EXAMPLE 60A**Preparation of compound 4004**

5

Step 1:

Alcohol **2a5** is transformed to compound **4004** using the thiophene **60a1** in the procedure of Step 1, Example 25A.

10 **EXAMPLE 61A****Preparation of intermediate 61a5**Step 1:

- 15 A mixture of dihydroxypyridine **61a1** (24 g, 216 mmol), K_2CO_3 (29.9 g, 216 mmol) and water (240 mL) is heated to 100°C until it becomes homogeneous. Solid I_2 (54.8 g, 216 mmol) is added portionwise (**caution**: evolution of gas!). When the iodine is consumed, the reaction is quenched with potassium hydrogen sulfate (216 mL, 216 mmol) which generates a precipitate. The precipitate is collected by filtration and
- 20 dried under a stream of N_2 to yield **61a2**.

Step 2:

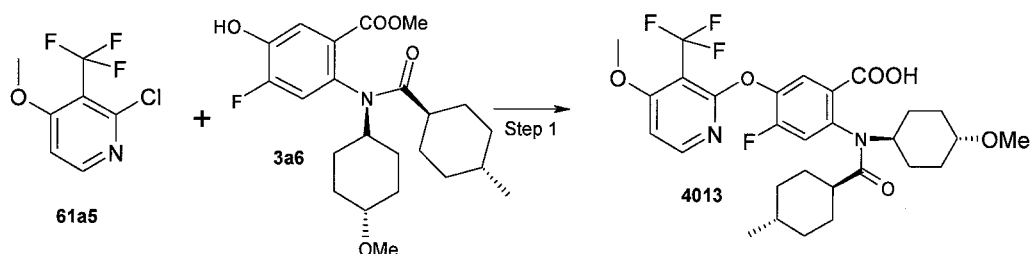
A mixture of the diol **61a2** (49.3 g, 208 mmol), DMF (0.161 mL, 2.08 mmol) and phosphorous oxychloride (252 mL, 2704 mmol) is heated to 90°C overnight. The reaction mixture is concentrated, quenched with saturated aqueous NaHCO₃,
5 extracted with DCM, dried and concentrated to yield **61a3**.

Step 3:

The di-chloride **61a3** (49 g, 179 mmol) and NaOMe (43.2 mL, 233 mmol) in MeOH (550 mL) is stirred at RT overnight. The reaction mixture is extracted with EtOAc and
10 water and concentrated. Upon standing, crystals are formed. The crystals are collected and washed with a small amount of iso-propyl ether. The crystals are transferred with heptane onto a glass filter and dried under a stream of air to yield **61a4**.

Step 4:

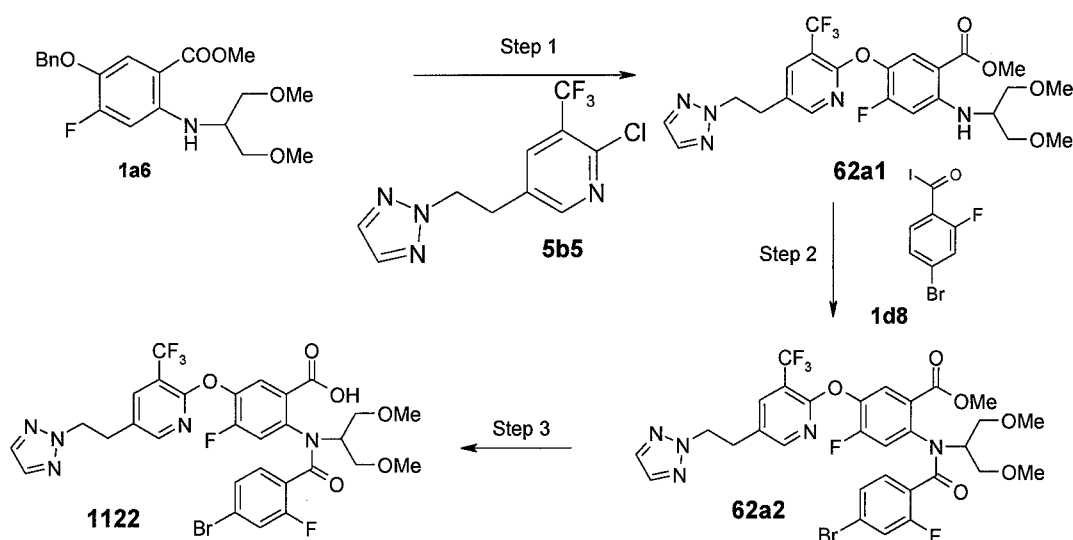
A solution/suspension of iodide **61a4** (1 g, 3.71 mmol), KF (0.216 g, 3.71 mmol) and CuI (0.707 g, 3.71 mmol) in NMP (10 mL) in a microwave tube is degassed with Ar. Methyl 2-chloro-2,2-difluoroacetate (3.64 mL, 34.5 mmol) is added and the vessel is closed under Ar and heated to 120°C for 30 min. in a microwave (**caution**: pressure
20 buildup observed, take appropriate caution). The mixture is cooled to RT and the excess pressure is slowly released. A brine solution is added; then the reaction mixture is extracted with Et₂O. The combined organic layers are washed with brine, dried and concentrated followed by multiple purifications by flash column chromatography to yield **61a5**.

EXAMPLE 61B**Preparation of compound 4013**Step 1:

Compound **4013** is generated via the reaction of compounds **61a5** and **3a6** using the procedure of Step 1, Example 16A.

EXAMPLE 62A

5 Preparation of compound **1122**



Step 1:

Pd/C (10%, 50 mg) is added to an EtOAc/MeOH (2:1, 9 mL) solution of compound **1a6** (640 mg, 1.69 mmol). The flask is closed with a septum, placed under vacuum, filled with hydrogen at atmospheric pressure and stirred at RT for about 2 h. The reaction vessel is placed under vacuum, filled with Ar and the solution is filtered over Celite®. DMSO (6 mL) is added to the solution, which is then concentrated under reduced pressure to a minimal volume. Cesium carbonate (661 mg, 2.03 mmole) is added, followed by chloropyridine **5b5** (422 mg, 1.53 mmol). The resulting mixture is heated at 75°C for about 12 h, cooled to RT, diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (10% to 40% EtOAc/hexanes) to afford compound **62a1**.

Step 2:

DMAP (7.7 mg, 0.063 mmol) and pyridine (0.152 mL, 1.88 mmol) are added to a

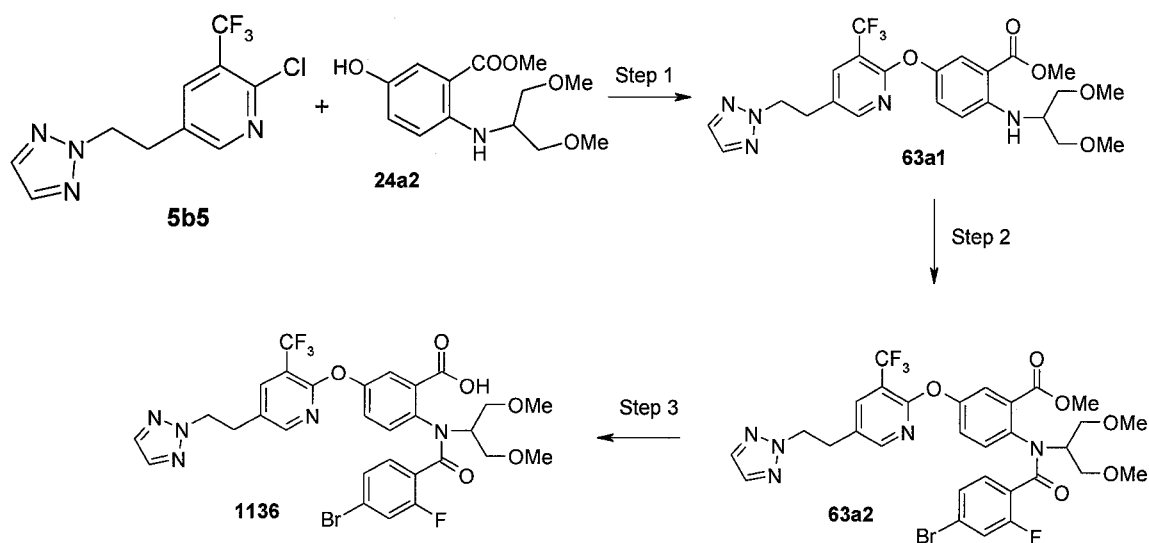
DCE (4 mL) solution of aniline **62a1** (166 mg, 0.315 mmol) and acid chloride **1d8** (299 mg, 1.259 mmol). The reaction mixture is heated at 150°C under microwave conditions, for 1 h, cooled to RT, diluted with EtOAc (100 mL) and washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL) and brine (2 x 50 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (80% EtOAc/hex) to afford compound **62a2**.

Step 3:

Aqueous 5 M NaOH (0.115 mL, 0.577 mmol) is added dropwise to a 0°C MeOH/THF solution (1:1, 2 mL) of ester **62a2** (63 mg, 0.086 mmol). The solution is stirred for about 2 h at RT, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1122**.

EXAMPLE 63A

Preparation of compound 1136



Step 1:

Potassium carbonate (414 mg, 3.00 mmol) is added to a RT DMSO (10 mL) solution of the chloropyridine **5b5** (380 mg, 1.37 mmol) and the phenol **24a2** (412 mg, 1.53 mmol). The reaction mixture is heated at 80°C overnight. The solution is cooled to RT, diluted with aqueous saturated sodium bicarbonate and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium

bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (30% to 75% EtOAc/hexanes) to afford **63a1**.

5 Step 2:

DMAP (1.2 mg, 0.010 mmol) and pyridine (0.024 mL, 0.31 mmol) are added to a DCE (2 mL) solution of aniline **63a1** (52.1 mg, 0.102 mmol) and acid chloride **1d8** (60.6 mg, 0.255 mmol). The reaction mixture is heated at 150°C in a microwave for 1 h, cooled to RT, diluted with EtOAc (100 mL) and washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL) and brine (2 x 50 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (80% to 100% EtOAc/hex) to afford compound **63a2**.

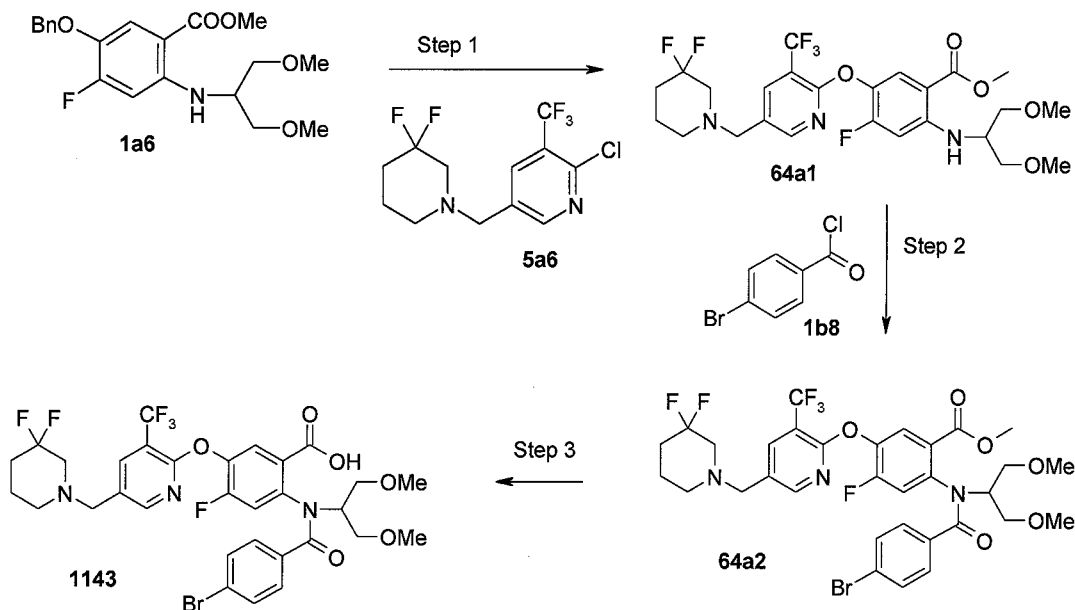
15 Step 3:

Aqueous 5 M NaOH (0.140 mL, 0.700 mmol) is added dropwise to a 0°C MeOH/THF solution (1:1, 2 mL) of ester **63a2** (50 mg, 0.070 mmol). The solution is stirred for about 2 h at RT, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1136**.

20

EXAMPLE 64A

Preparation of compound 1143

**Step 1:**

- Pd/C (10%, 24 mg) is added to an EtOAc/MeOH (2:1, 9 mL) solution of compound
- 5 **1a6** (715 mg, 1.89 mmol). The flask is closed with a septum, placed under vacuum, filled with hydrogen at atmospheric pressure and stirred at RT for about 2 h. The reaction vessel is placed under vacuum, filled with Ar and the solution is filtered over Celite®. DMSO (6 mL) is added to the solution, which is then concentrated under reduced pressure to a minimal volume. Cesium carbonate (739 mg, 2.27 mmole) is
- 10 added, followed by chloropyridine **5a6** (357 mg, 1.14 mmol). The resulting mixture is heated at 75°C for about 12 h, cooled to RT, diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure.
- 15 The residue is purified by column chromatography (20% to 60% EtOAc/hexanes) to afford compound **64a1**.

Step 2:

- DMAP (7.7 mg, 0.063 mmol) and pyridine (0.078 mL, 0.973 mmol) are added to a
- 20 DCE (4 mL) solution of aniline **64a1** (100 mg, 0.177 mmol) and acid chloride **1b8** (116 mg, 0.530 mmol). The reaction mixture is heated at 150°C under microwave conditions, for 1 h, cooled to RT, diluted with EtOAc (100 mL) and washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL) and brine (2 x

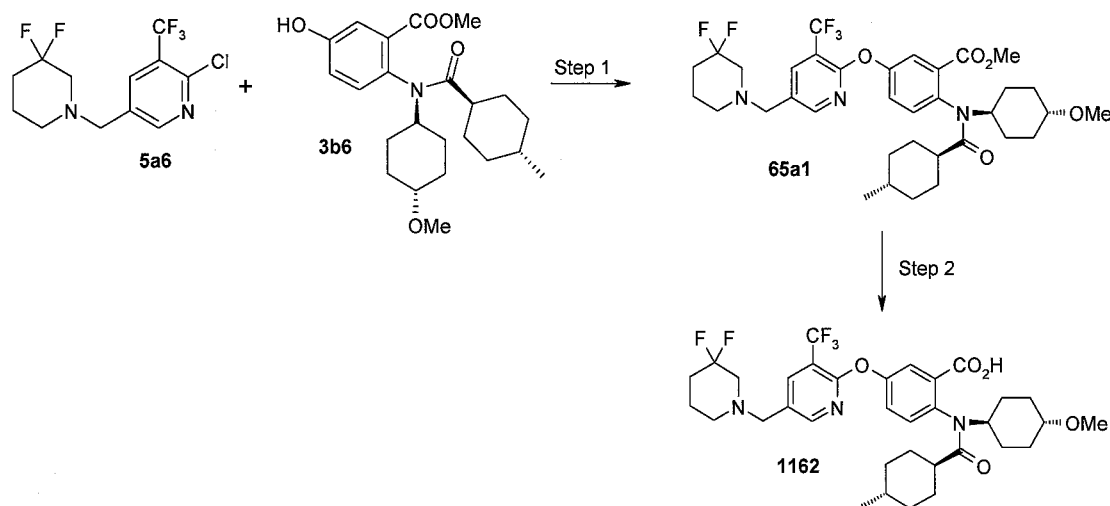
50 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude **64a2** is used directly in the next step.

Step 3:

- 5 Aqueous 5 M NaOH (0.695 mL, 3.475 mmol) is added dropwise to a 0°C THF/DMSO solution (2:1, 3 mL) of the crude ester **64a2**. The solution is stirred for about 2 h at RT, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1143**.

10 **EXAMPLE 65A**

Preparation of compound 1162



15 Step 1:

Potassium carbonate (103 mg, 0.744 mmol) is added to a DMSO (4 mL) solution of the chloropyridine **5a6** (175 mg, 0.558 mmol) and phenol **3b6** (150 mg, 0.372 mmol). The reaction mixture is stirred at 80°C overnight, cooled to RT, diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (30% EtOAc / hexanes to 100% EtOAc) to afford **65a1**.

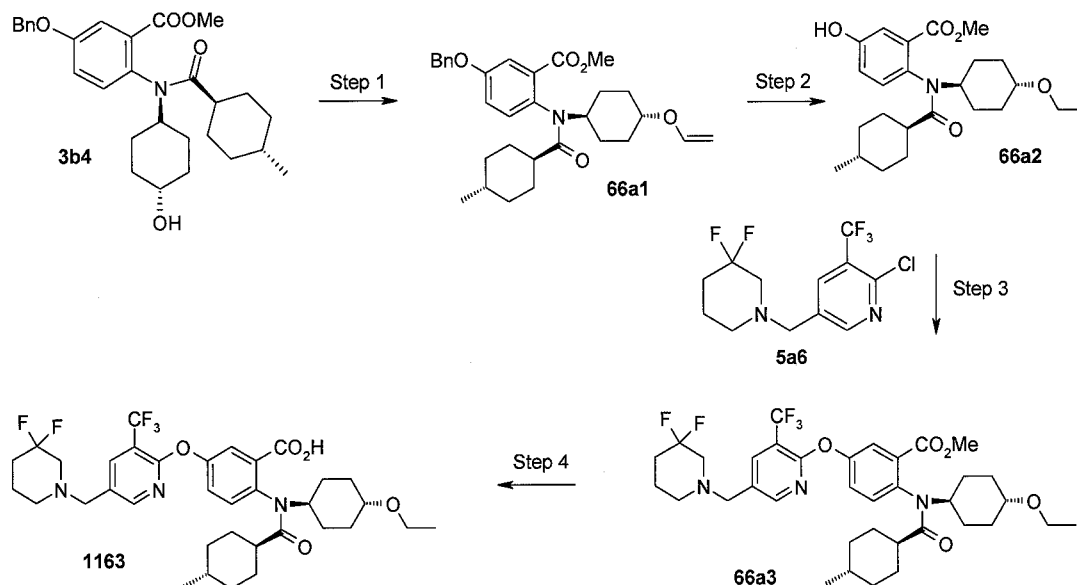
25 Step 2:

Aqueous 5 M NaOH (0.486 mL, 2.43 mmol) is added dropwise to a 0°C THF/MeOH

solution (2:1, 3 mL) of the ester **65a1** (166 mg, 0.243 mmol). The solution is stirred at RT for about 5 days, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1162**.

5 EXAMPLE 66A

Preparation of compound 1163



10 Step 1:

Palladium acetate (14 mg, 0.021 mmol) is added to a solution of 1,10-phenanthroline (3.6 mg, 0.020 mmol) in ethyl vinyl ether (5 mL). The mixture is stirred at RT for about 15 min to receive a solution of alcohol **3b4** (500 mg, 1.04 mmol) in ethyl vinyl ether (5 mL). The reaction mixture is heated at 60°C for about 46 h and cooled to RT. Silica gel is added and the mixture is concentrated under reduced pressure. The solid is applied onto a silica gel column and eluted with 20% EtOAc/hexanes to afford vinyl ether **66a1**.

Step 2:

20 Pd/C (10%, 14 mg) is added to a MeOH solution (10 mL) of the benzyl ether **66a1** (135 mg, 0.267 mmol). The reaction vessel is closed with a septum, placed under vacuum and filled back with hydrogen at atmospheric pressure. The reaction mixture is stirred overnight under hydrogen. The reaction vessel is placed under vacuum and filled back with Ar. The reaction mixture is filtered over Celite® and washed with

EtOAc (100 mL). The organic phase is concentrated under reduced pressure and the residue **66a2** is utilized crude in the following step.

Step 3:

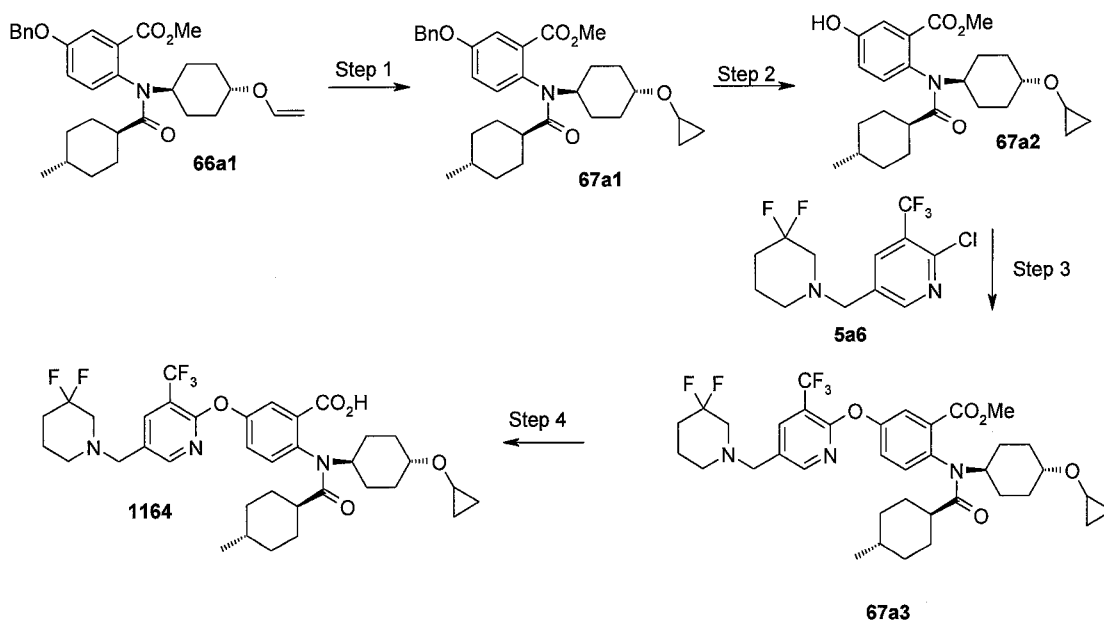
- 5 Potassium carbonate (71 mg, 0.512 mmol) is added to a DMSO (2 mL) solution of chloropyridine **5a6** (89 mg, 0.282 mmol) and phenol **66a2** (107 mg, 0.256 mmol). The reaction mixture is stirred at 80°C overnight, cooled to RT, diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with aqueous saturated sodium
- 10 bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (30% to 80% EtOAc/hexanes) to afford **66a3**.

Step 4:

- 15 Aqueous 5 M NaOH (0.122 mL, 0.610 mmol) is added dropwise to a 0°C THF/MeOH solution (2:1, 3 mL) of the ester **66a3** (85 mg, 0.122 mmol). The solution is stirred at RT for about 5 days, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1163**.

20 **EXAMPLE 67A**

Preparation of compound 1164



Step 1:

Diazomethane (5 mL, 0.6 M in ether) is added to an ice cold ether solution (10 mL) of vinyl ether **66a1** (170 mg, 0.336 mmol) and palladium acetate (10 mg, 0.045 mmol). The reaction mixture is stirred overnight at RT, filtered over Celite®, washed with EtOAc (50 mL) and concentrated under reduced pressure. The residue is purified by column chromatography (10% to 40% EtOAc in hexanes) to afford compound **67a1**.

10 Step 2:

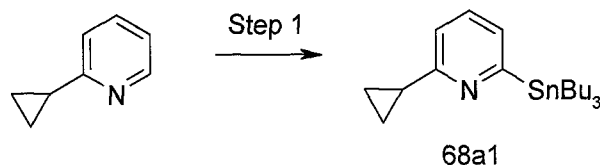
Pd/C (10%, 10 mg) is added to a MeOH solution (10 mL) of the benzyl ether **67a1** (132 mg, 0.254 mmol). The reaction vessel is closed with a septum, placed under vacuum and filled back with hydrogen at atmospheric pressure. The reaction mixture is stirred overnight under hydrogen. The reaction vessel is placed under vacuum and filled back with Ar. The reaction mixture is filtered over Celite® and washed with EtOAc (100 mL). The organic phase is concentrated under reduced pressure to afford crude **67a2** which is utilized crude in the following step.

Step 3:

20 Potassium carbonate (212 mg, 1.53 mmol) is added to a DMSO (10 mL) solution of chloropyridine **5a6** (241 mg, 0.768 mmol) and crude phenol **67a2**. The reaction mixture is stirred at 80°C overnight, cooled to RT, diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (30% to 80% EtOAc/hex) to afford **67a3**.

Step 4:

30 Aqueous 5 M NaOH (0.354 mL, 1.77 mmol) is added dropwise to a 0°C THF/MeOH solution (2:1, 3 mL) of the ester **67a3** (125 mg, 0.177 mmol). The solution is stirred at RT for about 5 days, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1164**.

EXAMPLE 68A**Preparation of intermediate 68a1**

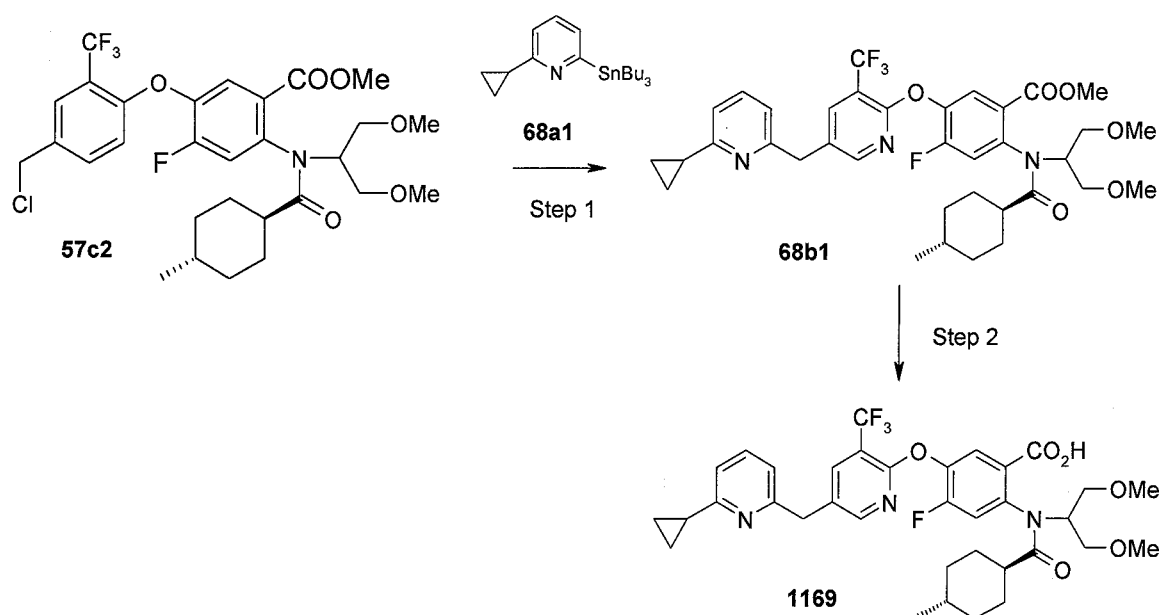
5

Step 1:

n-Butyllithium (2.1 M in hexanes, 8.82 mL, 18.5 mmol) is added dropwise to an ice cold hexanes (10 mL) solution of *N,N*-dimethylethanolamine (0.900 mL, 9.063 mmol). The reaction mixture is stirred at 0°C for about 30 min at which time a
10 hexanes solution (10 mL) of 2-cyclopropylpyridine (360 mg, 3.02 mmole) is added. The reaction mixture is stirred for about 45 min at 0°C and then cooled to -78°C to receive a hexanes solution (10 mL) of tributylstannyl chloride (3.44 g, 10.5 mmol). The mixture is stirred at -78°C for about 30 min, warmed to RT over about a 30 min period, diluted with water (100 mL) and extracted with ether (2 x 50 mL). The
15 combined organic phases are washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to obtain crude **68a1**.

EXAMPLE 68B**Preparation of compound 1169**

20



Step 1:

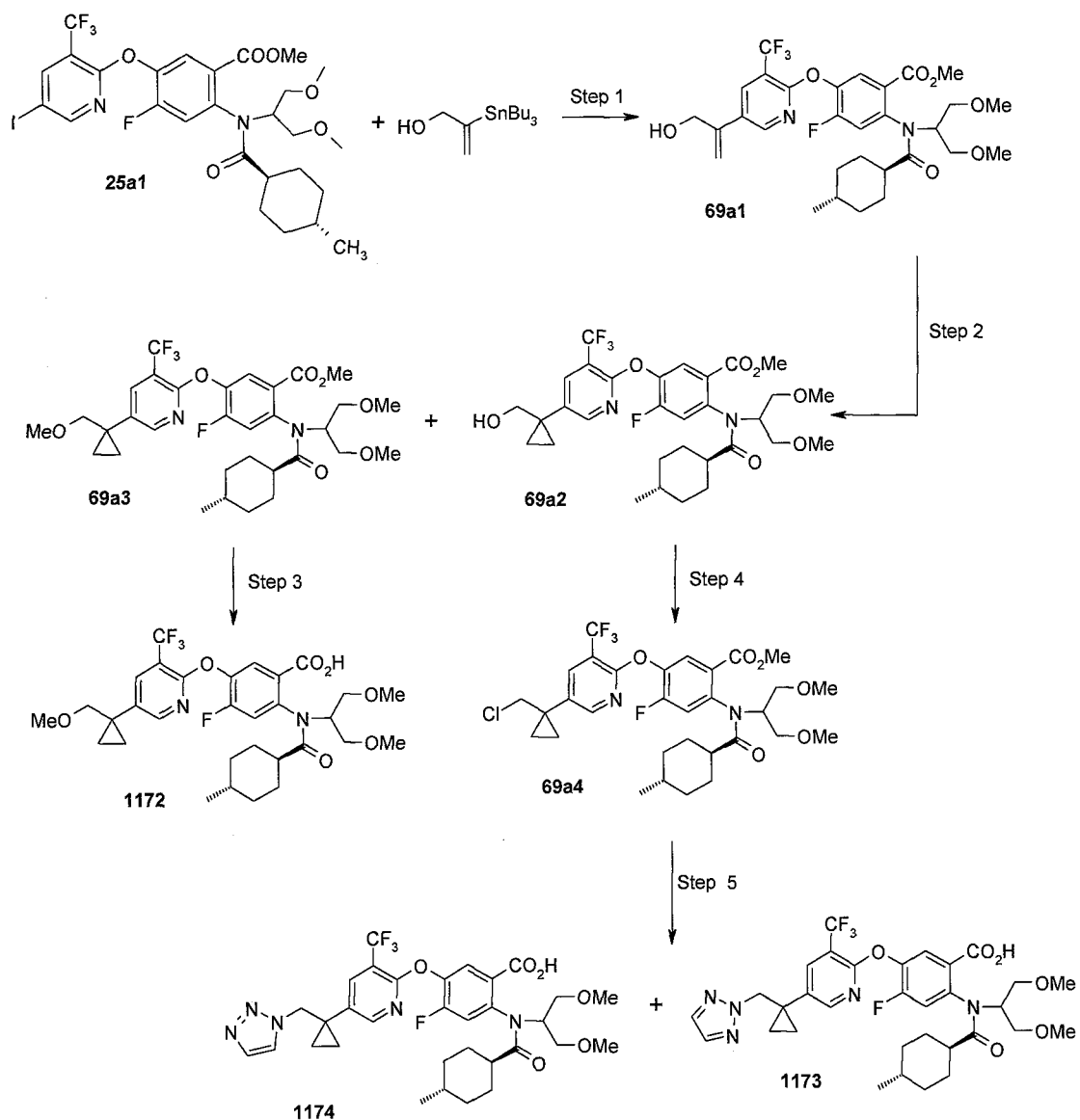
- 5 In a microwave tube, chloride **57c2** (102 mg, 0.169 mmol) is put in degassed DMF (2 mL, degassed by bubbling a volume of Ar while sonicating for about 10 min) along with stannyl **68a1** (241 mg, 0.177 mmol). Pd(PPh₃)₄ (49 mg, 0.017 mmol) is added, the tube is sealed and put in the microwave at 125°C for 20 min. The mixture is diluted in EtOAc and washed with water (2x) and brine (2x). The combined organics
- 10 are dried over MgSO₄, filtered and concentrated. The crude residue is passed on a short silica gel column (20% to 70% EtOAc in hex) to afford compound **68b1**.

Step 2:

- Aqueous 5 M NaOH (0.301 mL, 1.505 mmol) is added dropwise to a 0°C THF/DMSO solution (2:1, 3 mL) of ester **68b1** (85 mg, 0.124 mmol). The solution is stirred at RT
- 15 for about 5 days, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1169**.

EXAMPLE 69A

- 20 **Preparation of compounds 1172, 1173 and 1174**

**Step 1:**

Bis(tri-*tert*-butylphosphine)palladium (38 mg, 0.075 mmol) is added to a DMF solution (4 mL) of compound **25a1** (510 mg, 0.747 mmol) and stannane (285 mg, 0.822 mmol). The reaction mixture is degassed by bubbling Ar in the solution for about 15 min, stirred at 100°C for about 2 h, cooled to RT, diluted with aqueous saturated sodium bicarbonate and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (40% to 60% EtOAc in hexanes) to afford compound **69a1**.

Step 2:

- Diazomethane (5 mL, 0.6 M) is added to an ice cold ether solution (10 mL) of compound **69a1** (100 mg, 0.163 mmol) and palladium acetate (10 mg, 0.045 mmol). The reaction mixture is stirred overnight at RT, filtered over Celite®, washed with EtOAc (50 mL) and concentrated under reduced pressure. The residue is purified by column chromatography (50% to 90% EtOAc in hexanes) to afford methyl ether **69a3** and alcohol **69a2**.

Step 3:

- Aqueous 5 M NaOH (0.112 mL, 0.560 mmol) is added dropwise to a 0°C THF/MeOH solution (2:1, 3 mL) of ester **69a3** (36 mg, 0.056 mmol). The solution is stirred at RT for about 24 h, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1172**.

Step 4:

- Thionyl chloride (12 µL, 0.163 mmol) is added to a 0°C DMF solution (2 mL) of alcohol **69a2** (40 mg, 0.065 mmol), followed by one drop of DMF. The reaction mixture is stirred at RT for about 3 h, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude compound **69a4** is used directly in the following step.

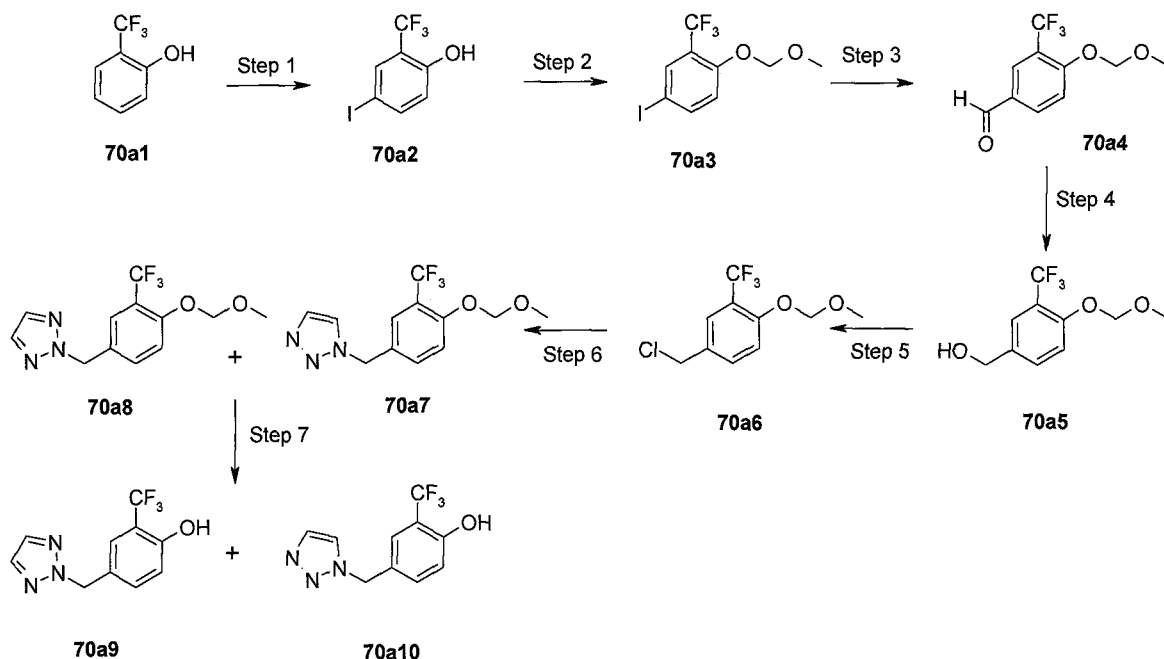
Step 5:

- Sodium hydride (60% in mineral oil, 5.2 mg, 0.130 mmol) is added to an ice cold solution of 1,2,3-triazole (8.9 mg, 0.130 mmol). The solution is transferred over an ice cold DMF solution of chloride **69a4** (41.8 mg, 0.065 mmol) and stirred at RT overnight. The reaction mixture is diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is dissolved in THF/MeOH (2:1, 3 mL) and cooled to 0°C. Aqueous 5 N sodium hydroxide (64 µL, 0.320 mmol) is added. The solution is stirred at RT for about 5 days, acidified with AcOH (1 mL) and purified by preparative

HPLC to afford **1174** and **1173**.

EXAMPLE 70A

Preparation of intermediate



5 Step 1:

Iodine monochloride (5.00 g, 30.8 mmol) is slowly added to a RT glacial acetic acid solution (40 mL) of 2-hydroxybenzotrifluoride **70a1** (5.00 g, 30.8 mmol). The reaction mixture is stirred overnight at RT then poured over water (200 mL). The mixture is extrated with EtOAc (3 x 100 mL) and the combined organic phases are washed with
 10 water (100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (100% hexanes then 2% to 20% EtOAc /hexanes) to afford compound **70a2**.

Step 2:

15 Sodium hydride (60% in mineral oil, 312 mg, 7.82 mmol) is added to a 0°C DMF solution of phenol **70a2** (1.50 g, 5.21 mmol). he solution is stirred at 0°C for about 5 min and chloromethylmethylether (514 µL, 6.77 mmole) is added. The reaction mixture is stirred at RT overnight, diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic
 20 phases are washed with water (2 x 50 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by

column chromatography (100% hexanes then 2% to 20% EtOAc / hexanes) to afford compound **70a3**.

Step 3:

- 5 *n*-Butyllithium (2.5 M in hexanes, 1.66 mL, 4.14 mmol) is slowly added to a -78 °C ether solution (35 mL) of iodophenol **70a3** (1.18 g, 3.54 mmol). The reaction mixture is stirred for about 15 min at -78 °C and DMF is added (418 µL, 5.40 mmol). The reaction mixture is stirred at RT for about 1 h, diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic
- 10 phases are washed with water (2 x 50 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (100% hexanes then 2% to 20% EtOAc /hexanes) to afford compound **70a4**.

Step 4:

- 15 Sodium borohydride (143 mg, 3.79 mmol) is added to a 0°C MeOH (30 mL) solution of aldehyde **70a4** (740 mg, 3.16 mmol). The reaction is stirred at 0°C for about 2 h, diluted with saturated aqueous sodium bicarbonate (50 mL), concentrated under reduced pressure and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with brine (100 mL), dried over Na₂SO₄, filtered and
- 20 concentrated under reduced pressure. The crude residue is purified by column chromatography (100% hexanes then 2% to 20% EtOAc / hexanes) to afford compound **70a5**.

Step 5:

- 25 Thionyl chloride (377 µL, 5.17 mmol) is added to a 0°C DCM (20 mL) solution of alcohol **70a5** (610 mg, 2.58 mmol). The reaction mixture is stirred at RT for about 1 h, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude
- 30 residue **70a6** is used directly in the next step.

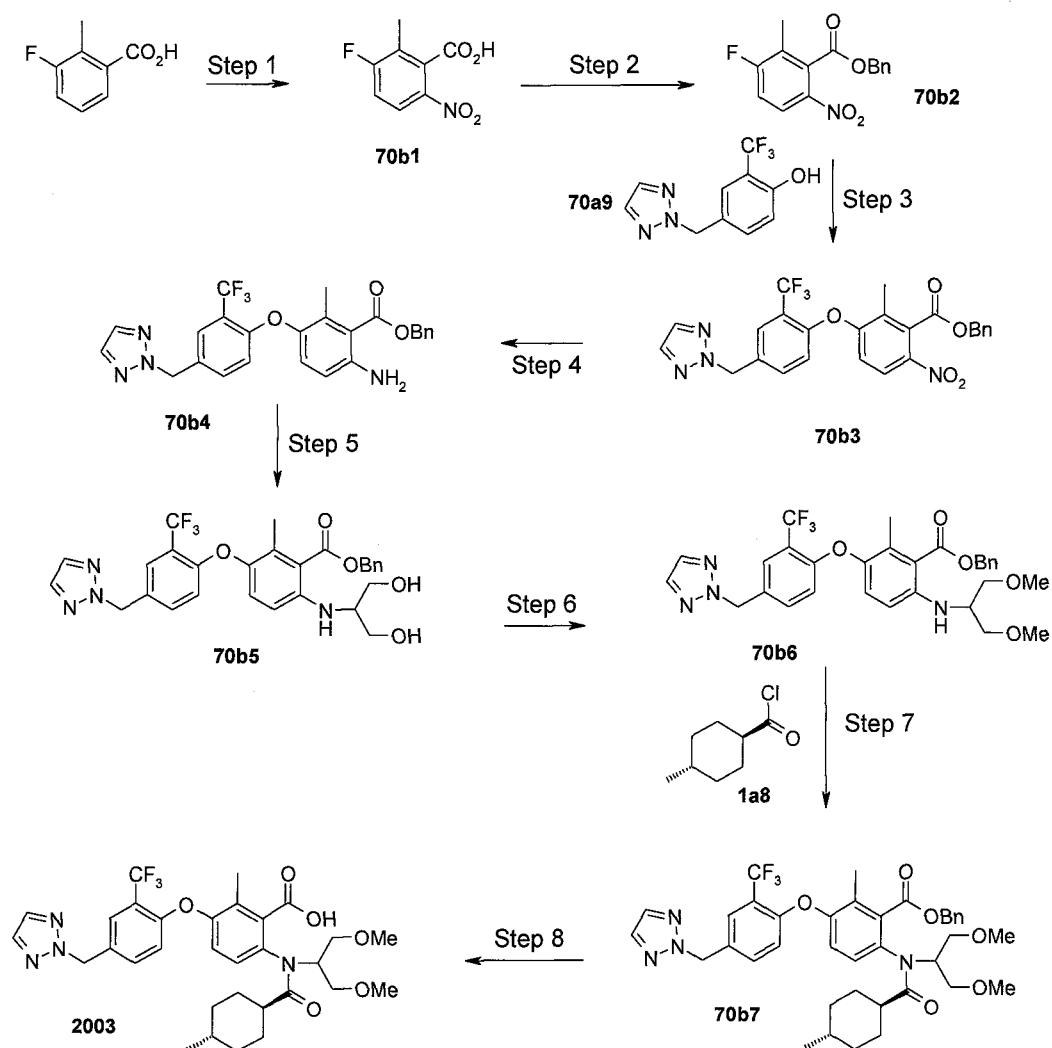
Step 6:

Sodium hydride (60% in mineral oil, 196 mg, 4.90 mmol) is added to a 0°C DMF solution (3 mL) of 1,2,3-triazole (336 mg, 4.87 mmol). The reaction mixture is stirred

at 0°C for about 30 min and transferred over a 0°C DMF solution (20 mL) of benzyl chloride **70a6** (620 mg, 2.44 mmol). The reaction mixture is stirred for about 2 h at RT, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with brine (100 mL),
5 dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (100% hexanes then 20% to 80% EtOAc / hexanes) to afford a mixture of compounds **70a7** and **70a8**.

Step 7:

10 Aqueous 1 N HCl (2.0 mL) is added to a 0°C THF solution (10 mL) of compounds **70a7** and **70a8** (699 mg, 2.44 mmol). The reaction mixture is warmed up to RT and then heated at 65 °C for about 3 h. The reaction mixture is cooled to RT, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with brine (100 mL), dried over
15 Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (30% EtOAc / hexanes to 100% EtOAc) to afford a mixture of compounds **70a9** (elutes first) and **70a10**.

EXAMPLE 70B**Preparation of compound 2003****5 Step 1:**

3-fluoro-2-methylbenzoic acid (5.0 g, 32.4 mmol) is dissolved in sulfuric acid (35 mL) and the resulting mixture is cooled to 0°C. Nitric acid (4.0 mL) is added dropwise over about a 10 min period. The reaction mixture is stirred at 0°C for about 2 h, poured over ice and extracted with EtOAc (2 x 50 mL). The combined organic phases are dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude **70b1**.

Step 2:

Potassium carbonate (2.05 g, 14.8 mmol) is added to a RT DMF (60 mL) solution of acid **70b1** (1.48 g, 7.32 mmol), followed by benzyl bromide (1.06 mL, 8.91 mmol).

The reaction mixture is stirred at 80°C overnight, cooled to RT, poured over water and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (20% EtOAc in hexanes) to afford ester **70b2**.

Step 3:

Cesium carbonate (1.41 g, 4.36 mmol) is added to a DMSO solution of ester **70b2** (1.050 g, 3.63 mmol) and phenol **70a9** (883 mg, 3.63 mmol). The reaction mixture is stirred for about 2 h at 75°C. After cooling to RT, the solution is diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (20% to 50% EtOAc/hexanes) to afford **70b3**.

Step 4:

Saturated aqueous ammonium chloride (20 mL) is added to a RT 2-propanol (20 mL) solution of nitro **70b3** (855 mg, 1.67 mmol). Iron powder (652 mg, 11.5 mmol) is added and the resulting reaction mixture is stirred at 60°C for about 3 h. The mixture is cooled to RT, filtered through Celite® and washed with EtOAc. The organic phase is collected, washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. As approximately half of the material is saponified to the acid, the crude residue is redissolved in DMF (50 mL) and potassium carbonate (461 mg, 3.37 mmol) and benzyl bromide (0.245 mL, 2.02 mmol) are added. The reaction mixture is stirred at 80°C overnight, cooled to RT, poured over water and extracted with EtOAc (2 x 100 mL). The combined organic phases are washed with brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude aniline **70b4** is used directly in the next step.

Step 5:

The crude aniline **70b4** (550 mg, 1.14 mmol) is dissolved in MeOH (1 mL) and 2 M HCl in ether (1 mL) is added. The mixture is stirred at RT for about 1 h and concentrated under reduced pressure. The resulting residue is dissolved in MeOH (10 mL) and a MeOH (3 mL) solution of dihydroxyacetone (649 mg, 7.21 mmol) is

added. The reaction mixture is stirred at RT for about 1 h and a MeOH solution (3 mL) of sodium cyanoborohydride (266 mg, 4.24 mmol) is added. The reaction mixture is stirred at RT for about 1 h, diluted with aqueous saturated sodium bicarbonate (50 mL), concentrated under reduced pressure to a minimal volume and
5 extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (50% EtOAc/hex to 100% EtOAc) to afford **70b5**.

10 Step 6:

A DMF suspension (2 mL) of sodium hydride (95%, 44 mg, 1.74 mmol) is added to a 0°C DMF solution of compound **70b5** (440 mg, 0.791 mmol) and iodomethane (247 µL, 3.95 mmol). The reaction mixture is stirred at 0°C for about 1 h and more sodium hydride is then added (95%, 44 mg, 1.74 mmol in 2 mL of DMF). The reaction
15 mixture is stirred at 0°C for about 1 h, diluted with aqueous saturated ammonium chloride (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude **70b6** is used directly in the next step without further purification.

20

Step 7:

DMAP (1.6 mg, 0.014 mmol) is added to a DCE (1 mL) solution of aniline **70b6** (40 mg, 0.068 mmol), acid chloride **1a8** (44 mg, 0.27 mmol) and pyridine (32 µL, 0.41 mmol). The reaction mixture is heated at 150°C for about 45 min in a microwave.
25 The reaction mixture is cooled to RT and then pyridine (32 µL, 0.41 mmol) and acid chloride **1a8** (44 mg, 0.27 mmol) are added. The reaction mixture is resubmitted to microwave conditions (45 min at 150°C), cooled to RT, diluted with aqueous 1 N HCl (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed with aqueous 1 N HCl (50 mL), saturated aqueous sodium bicarbonate (2 x
30 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (20% EtOAc/hex to 100% EtOAc) to afford **70b7**.

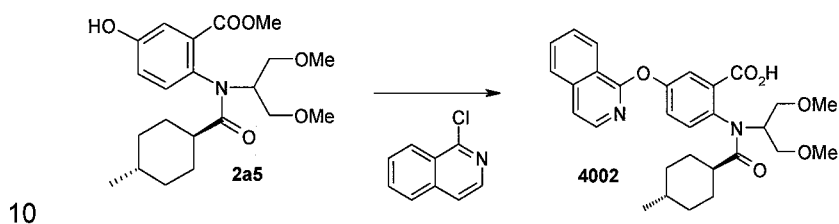
Step 8:

35 Palladium 10% on charcoal (15 mg) is added to an EtOAc/MeOH (2:1, 6 mL)

solution of the benzyl ester **70b7** (12 mg, 0.017 mmol). The reaction mixture is evacuated and filled back with hydrogen at atmospheric pressure. The reaction mixture is stirred at RT for about 15 min, filtered over Celite®, washed with EtOAc and concentrated under reduced pressure. The crude residue is purified by
5 preparative HPLC to afford **2003**.

EXAMPLE 71A

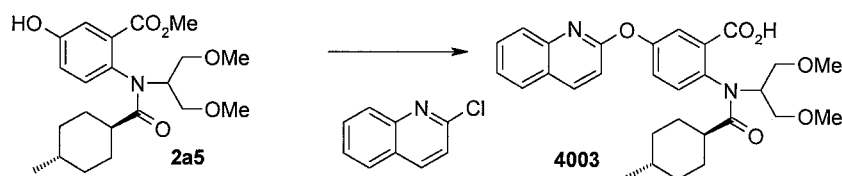
Preparation of compound 4002



Potassium carbonate (277 mg, 0.854 mmol) is added to a DMSO solution (5 mL) of phenol **2a5** (160 mg, 0.407 mmol) and chloroisoquinoline (73 mg, 0.477 mmol). The reaction mixture is stirred at 150°C for about 10 min, cooled to RT and filtered. To
15 the resulting solution is added aqueous 2.5 N NaOH (0.3 mL, 0.750 mmol). The reaction mixture is stirred at RT for about 3 h, acidified with glacial AcOH (2 mL) and purified by preparative HPLC to afford compound **4002**.

EXAMPLE 72A

20 Preparation of compound 4003



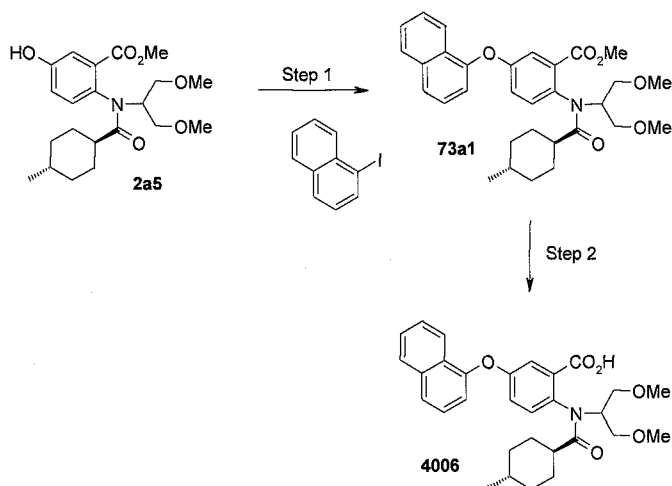
Cesium carbonate (208 mg, 0.640 mmol) is added to a DMSO solution (5 mL) of
25 phenol **2a5** (120 mg, 0.305 mmol) and chloroquinoline (50 mg, 0.305 mmol). The reaction mixture is stirred at 150°C for about 10 min, cooled to RT and filtered. To the resulting solution is added aqueous 2.5 N NaOH (0.3 mL, 0.750 mmol). The reaction mixture is stirred at RT for about 3 h, acidified with glacial AcOH (2 mL) and

purified by preparative HPLC to afford compound **4003**.

EXAMPLE 73A

Preparation of compound **4006**

5



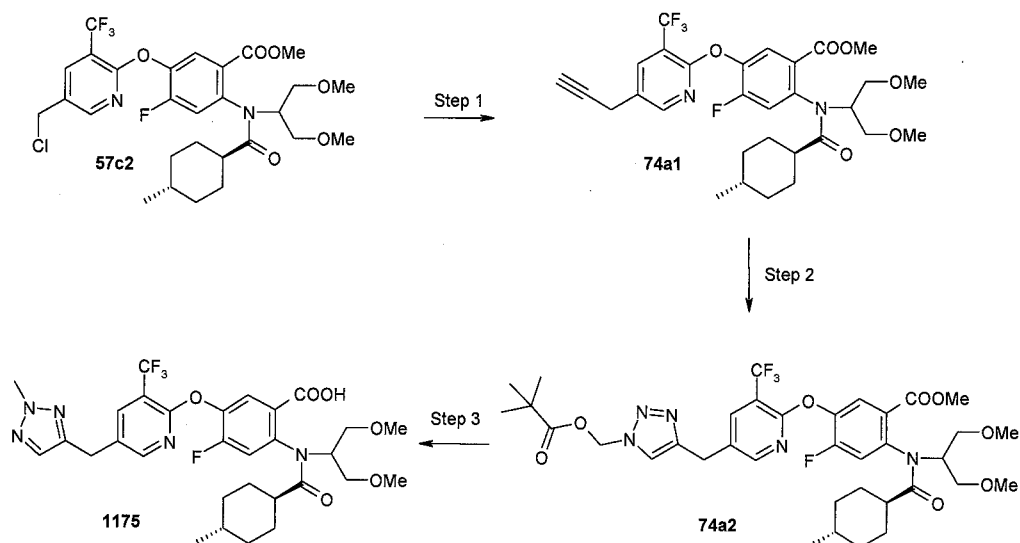
Step 1:

Copper (I) chloride (13 mg, 0.13 mmol) is added to a NMP solution (3 mL) of phenol **2a5** (100 mg, 0.254 mmol), iodide (77 mg, 0.35 mmol), cesium carbonate (166 mg, 0.508 mmol) and 2,2,6,6-tetramethylheptane-3,5-dione (5 μ L, 0.025 mmol). The reaction mixture is evacuated and filled with nitrogen. The cycle is repeated 5 times then the reaction mixture is stirred at 120°C for about 2 h, cooled to RT, diluted with saturated aqueous sodium bicarbonate and extracted with EtOAc (50 mL). The organic phase is washed with aqueous saturated sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (20% EtOAc/hex to 60% EtOAc) to afford **73a1**.

Step 2:

Aqueous 5 M NaOH (0.265 mL, 1.32 mmol) is added dropwise to a 0°C THF/DMSO solution (1:1, 2 mL) of ester **73a1** (46 mg, 0.089 mmol). The solution is stirred at 40°C for about 2 h, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **4006**.

25

EXAMPLE 74A**Preparation of compound 1175****Step 1:**

To a solution of chloride **57c2** (200 mg, 0.33 mmol) in DMF (2 mL) are added
 5 trimethylsilylacetylene (162 mg, 1.65 mmol), CuI (6.3 mg, 0.033 mmol), Et_3N (0.230 mL, 1.65 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (38 mg, 0.033 mmol) at RT. This mixture is stirred at 120°C in the microwave for 10 min. TBAF (1.65 mL, 1 M solution in THF) is added at RT and the reaction mixture is stirred for about 30 min. A saturated aqueous solution of NH_4Cl is added and the mixture is extracted with Et_2O (3x). The organic layers are
 10 combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue is then purified by flash chromatography using (20:80 to 60:40) EtOAc/Hex to afford compound **74a1**.

Step 2:

To a solution of alkyne **74a1** (123 mg, 0.21 mmol) in water (1 mL) is added azide
 15 **44a2** (97 mg, 0.62 mmol) at RT. This mixture is stirred at 120°C for about 3 h, then at 85°C for about 16 h. The reaction mixture is extracted with Et_2O (3x). The organic layers are combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered under vacuum and concentrated. The crude residue is purified by flash chromatography
 20 using (20:80 to 70:30) EtOAc/Hex to afford compound **74a2**.

Step 3:

To a solution of ester **74a2** in MeOH (1 mL) is added an aqueous NaOH solution (5 N, 0.024 mL, 0.12 mmol) at RT. The mixture is stirred for about 5 h before being acidified with 1 M HCl and extracted with EtOAc (4x). The combined fractions are dried and concentrated. The residue is re-dissolved in MeOH (2 mL) and

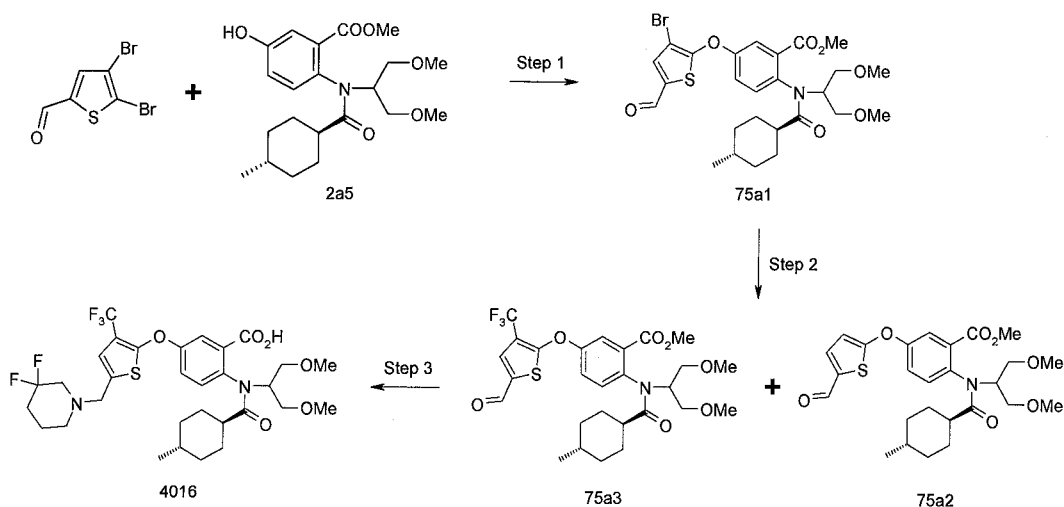
5 (trimethylsilyl)diazomethane (0.120 mL, 2 M solution in Et₂O) is added at 0°C. The reaction mixture is stirred for about 1 h at 0°C, then concentrated. The residue is re-dissolved in a THF (1 mL) / MeOH (1 mL) mixture and an aqueous NaOH solution (5 N, 0.024 mL, 0.12 mmol) is added at RT. The mixture is stirred for about 3 h, then concentrated. The residue is re-dissolved in a MeOH (1 mL) / AcOH (1 mL) mixture

10 and purified by preparative HPLC. The fractions are combined and solvent removed by lyophilization to afford pure compound **1175**.

EXAMPLE 75A

Preparation of compound 4016

15



Step 1:

Cesium carbonate (2.48 g, 7.62 mmol) is added to a DMSO solution (10 mL) of the phenol **2a5** (1.78 g, 6.61 mmol) and 4,5-dibromo-thiophene-2-carbaldehyde (35 mL, 5.08 mmol). The reaction mixture is stirred at 80°C for about 16 h, cooled to RT, poured over water and extracted with Et₂O (3 x 50 mL). The combined organic phases are concentrated under reduced pressure. The crude residue is purified by column chromatography (30% to 70% EtOAc in hexanes) to afford compound **75a1**.

20

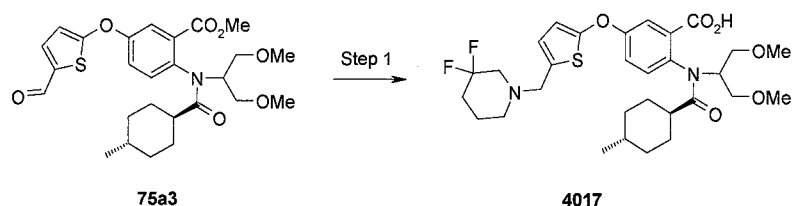
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Step 2:

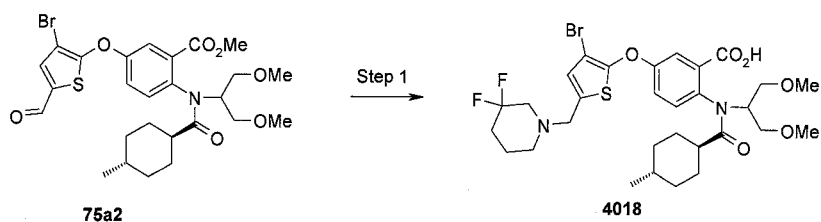
Sodium trifluoroacetate (383 mg, 2.82 mmol) is added to a NMP solution (2 mL) of the bromide **75a1** (410 mg, 0.704 mmol) and copper iodide (268 mg, 1.41 mmol). The reaction mixture is stirred at 160°C in the microwave for 10 min, then at 180°C for another 10 min and cooled to RT. The reaction mixture was poured over water and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (40% to 70% EtOAc in hexanes) to afford compound **75a2** and compound **75a3**.

Step 3:

Compound **75a3** is transformed to compound **4016** using the procedure in Steps 2 and 3, Example 37A.

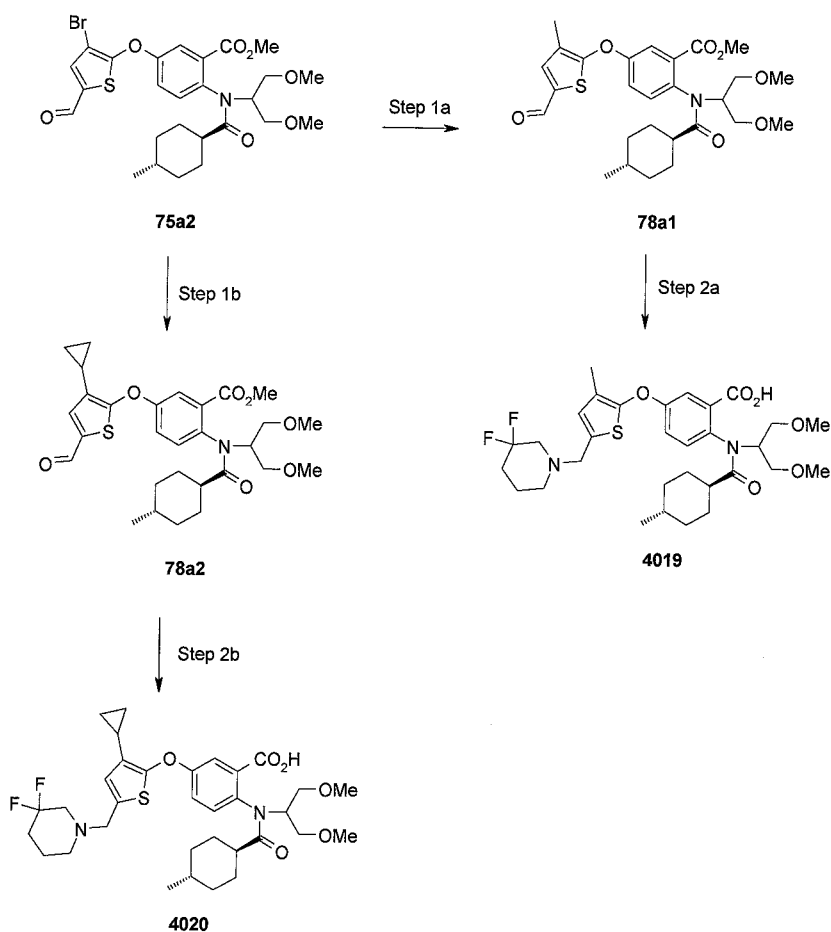
EXAMPLE 76A**Preparation of compound 4017****Step 1:**

Compound **75a3** is transformed to compound **4017** using the procedure described in Step 3, Example 75A.

EXAMPLE 77A**Preparation of compound 4018**

Step 1:

Compound **75a2** is transformed to compound **4018** using the procedure described in Step 3, Example 75A.

5 **EXAMPLE 78A****Preparation of compounds 4019 and 4020**10 Step 1a:

Pd(PPh₃)₄ (1.35 mg, 0.005 mmol) and sodium carbonate (2 M solution in water, 0.375 mL, 0.750 mmol) are added to a DMF solution (1 mL) of the bromide **75a2** (150 mg, 0.258 mmol) and trimethylboroxine (97 mg, 0.773 mmol). The reaction mixture is stirred at 120°C in the microwave for 20 min, cooled to RT, poured over water and extracted with Et₂O (3 x 50 mL). The combined organic phases are washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (40% to

80% EtOAc in hexanes) to afford compound **78a1**.

Step 2a:

Compound **78a1** is transformed to compound **4019** using the procedure described in
5 Steps 2 and 3, Example 37A.

Step 1b:

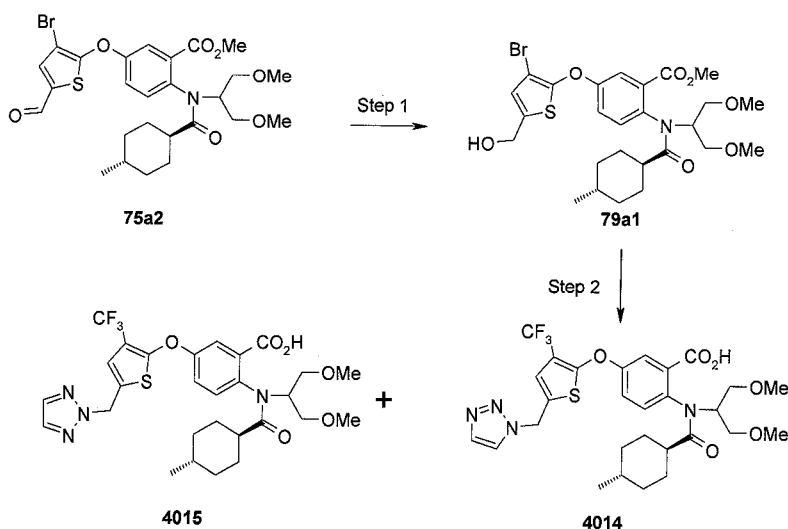
Pd(PPh₃)₄ (1.35 mg, 0.005 mmol) and sodium carbonate (2 M solution in water,
0.386 mL, 0.773 mmol) are added to a DMF solution (1 mL) of the bromide **75a2**
10 (150 mg, 0.258 mmol) and cyclopropylboronic acid (66 mg, 0.773 mmol). The
reaction mixture is stirred at 120°C in the microwave for 20 min, cooled to RT,
poured over water and extracted with Et₂O (3 x 50 mL). The combined organic
phases are washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and
concentrated under reduced pressure. The crude residue is purified by column
15 chromatography (40% to 80% EtOAc in hexanes) to afford compound **78a2**.

Step 2b:

Compound **78a2** is transformed to compound **4020** using the procedure described in
Steps 2 and 3, Example 37A.
20

EXAMPLE 79A

Preparation of compound 4014 and 4015

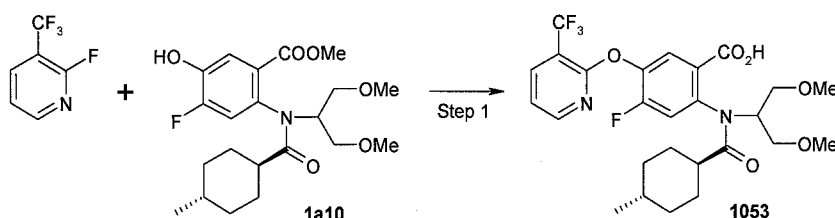


Step 1:

Compound **75a2** is transformed to compound **79a1** using the procedure described in Step 1, Example 57C.

5 Step 2:

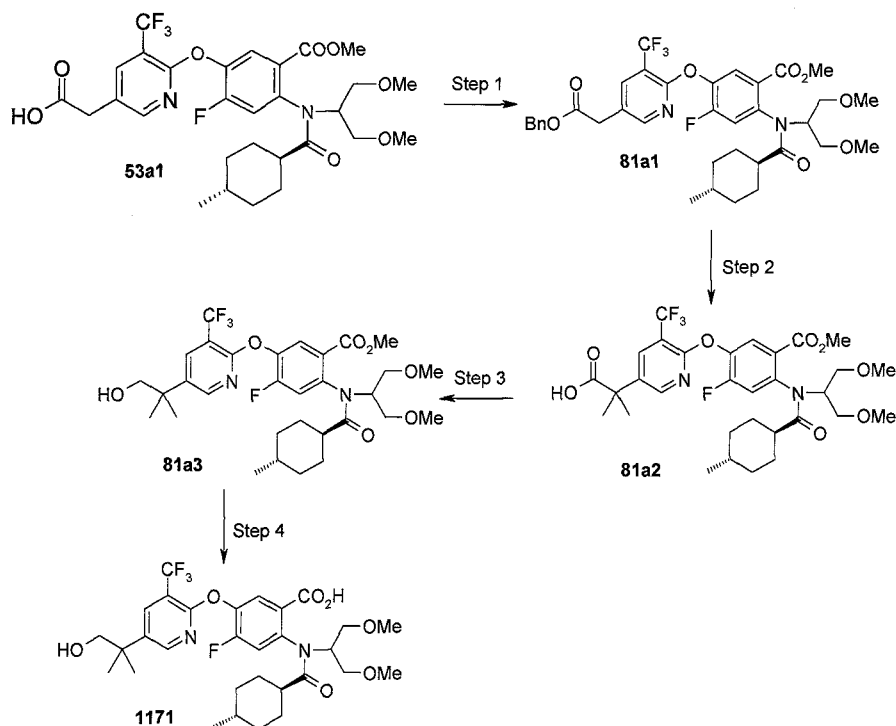
Compound **79a1** is transformed to compounds **4014** and **4015** using the procedure described in Step 1, Example 57D.

EXAMPLE 80A10 **Preparation of compound 1053**Step 1:

Phenol **1a10** (16.8 mg, 0.041 mmol) is combined with K_2CO_3 (16.9 mg, 0.122 mmol) and 2-fluoro-3-trifluoromethylpyridine (39.0 mg, 0.24 mmol) in DMSO (1 mL). The mixture is heated under Ar at 75°C until complete conversion, then cooled to RT. Water and DCM are added, the mixture is extracted with DCM (3x) and the combined organic fractions are concentrated under reduced pressure. The crude residue is dissolved in a THF (1 mL)/MeOH (0.5 mL)/H₂O (0.5 mL) mixture and an aqueous NaOH solution (10 N, 41 μ L, 0.41 mmol) is added. The mixture is stirred overnight before being acidified with AcOH, filtered, and injected onto a preparative HPLC to isolate compound **1053**.

EXAMPLE 81A**Preparation of compound 1171**

25

**Step 1:**

Potassium carbonate (67 mg, 0.488 mmol) is added to a DMF solution (2 mL) of the acid **53a1** (150 mg) and benzyl bromide (35 μ L, 0.293 mmol). The reaction mixture is stirred at 80°C overnight, cooled to RT, poured over water and extracted with EtOAc (3 x 50 mL). The combined organic phases are washed successively with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is purified by column chromatography (20 % EtOAc in hexanes) to afford compound **81a1**.

Step 2:

Sodium hydride (13 mg, 0.511 mmol) is added to a 0°C DMF (12 mL) solution of ester **81a1** (120 mg, 0.170 mmol) followed by iodomethane (42 μ L, 0.681 mmol). The reaction mixture is stirred at RT for about 2 h, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue is dissolved in 80% EtOAc in hexanes and passed through a silica plug. The resulting organic phase is concentrated under reduced pressure to obtain a residue which is redissolved in

EtOH (25 mL). The reaction flask is evacuated and filled back with hydrogen at atmospheric pressure. The mixture is stirred at RT for about 4 h, filtered through Celite®, washed with EtOH and concentrated under reduced pressure to afford crude **81a2** which is used directly in the next step.

5

Step 3:

Isobutyl chloroformate (30 µL, 0.23 mmol) is added to a 0°C THF (2 mL) solution of acid **81a2** (100 mg, 0.156 mmol) and triethylamine (39 µL, 0.28 mmol). The reaction mixture is stirred at 0°C for about 30 min and filtered directly over a water (0.2 mL) suspension of sodium borohydride (18 mg, 0.467 mmol). The reaction mixture is stirred at 0°C for about 20 min, diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases are washed successively with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude **81a3**.

15

Step 4:

Aqueous 5 M NaOH (1.0 mL, 5.0 mmol) is added dropwise to a 0°C DMSO solution (2 mL) of ester **81a3** (20 mg, 0.032 mmol). The solution is stirred at RT for about 2 h, acidified with AcOH (1 mL) and purified by preparative HPLC to afford compound **1171**.

20

EXAMPLE 82

Inhibition of NS5B RNA dependent RNA polymerase activity

Representative compounds of the invention are tested for inhibitory activity against the hepatitis C virus RNA dependent polymerase (NS5B), according to the assay described in WO 2007/087717, herein incorporated by reference.

25

EXAMPLE 83

SPECIFICITY OF NS5B RNA DEPENDENT RNA POLYMERASE INHIBITION

Representative compounds of the invention are tested for inhibitory activity against polio virus RNA dependent RNA polymerase and calf thymus DNA dependent RNA polymerase II as described in McKercher et al., (2004) Nucleic Acids Res. **32**: 422-431, herein incorporated by reference.

35

EXAMPLE 84**Cell-based luciferase reporter HCV RNA Replication Assay**

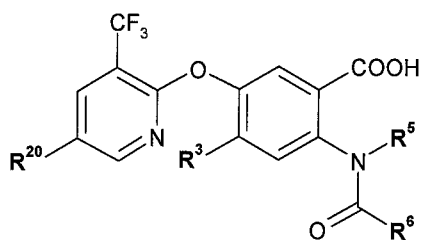
Representative compounds of the invention are tested for activity as inhibitors of hepatitis C virus RNA replication in cells expressing a stable subgenomic HCV replicon, using the assay described in WO 2005/028501, herein incorporated by reference.

TABLES OF COMPOUNDS

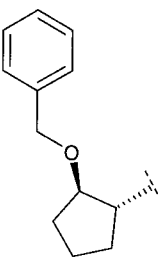
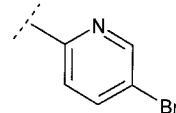
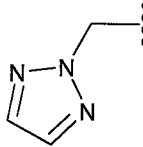
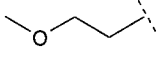
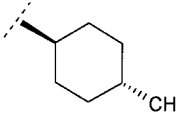
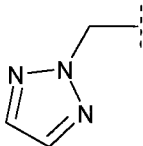
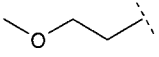
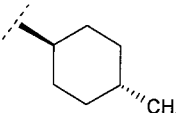
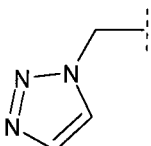
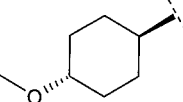
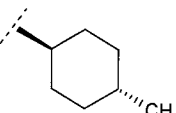
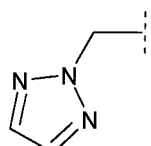
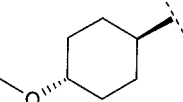
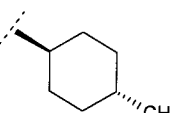
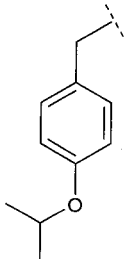
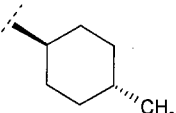
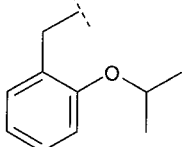
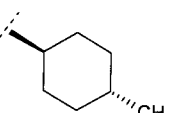
The following tables list compounds representative of the invention. Representative compounds listed in Tables 1 and 4 below are tested in the assay of Example 82 and are found to have IC₅₀ value below 30 µM. Representative compounds listed in Tables 1 and 4 below are tested in the assay of Example 84 and are found to have a EC₅₀ values below 30 µM.

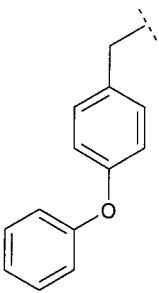
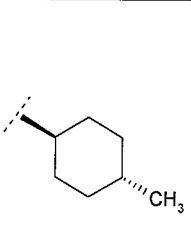
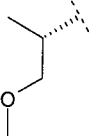
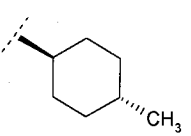
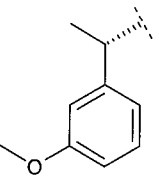
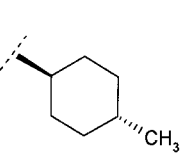
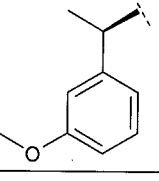
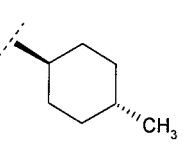
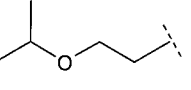
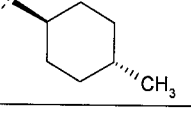
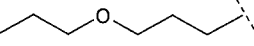
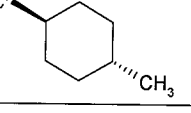
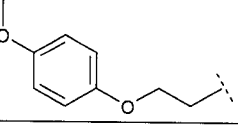
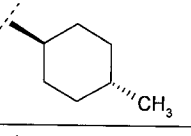
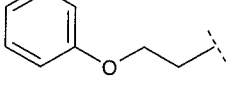
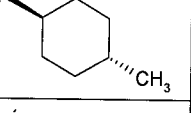
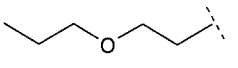
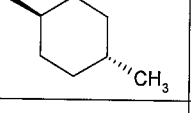
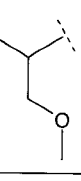
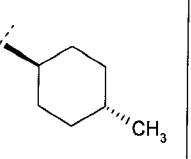
Retention times (t_R) for each compound are measured using the standard analytical HPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary when measured, for example, on different HPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions. The synthetic method used to generate each compound in Tables 1 to 4 is identified in the table. A person skilled in the art will recognize that obvious modifications to the synthetic methods may be required to generate each of the specific compounds listed in Tables 1 to 4.

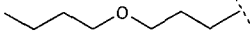
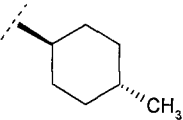
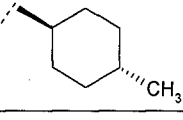
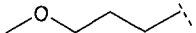
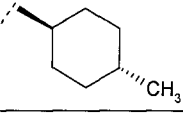
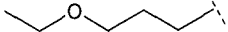
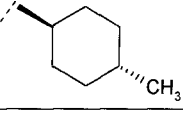
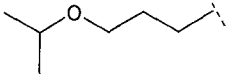
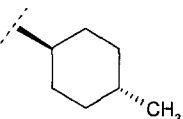
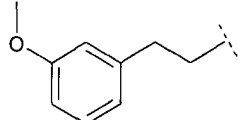
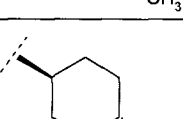
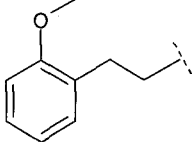
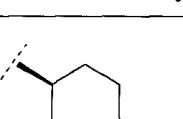
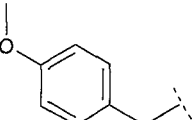
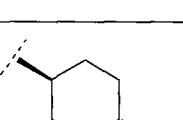
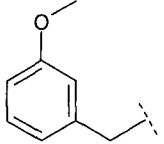
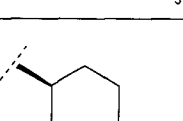
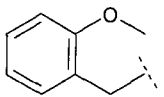
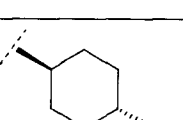
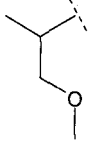
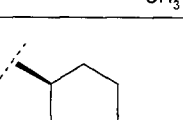
Table 1



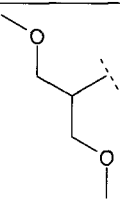
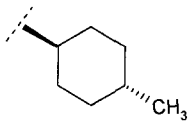
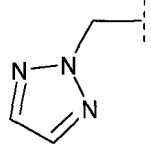
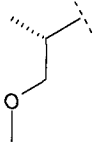
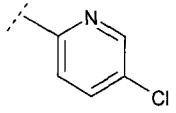
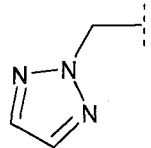
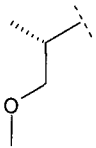
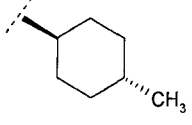
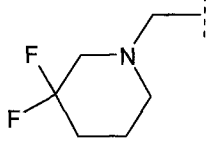
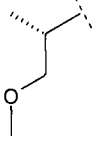
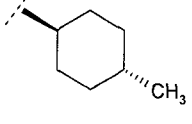
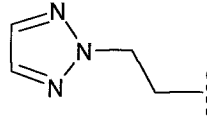
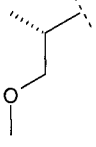
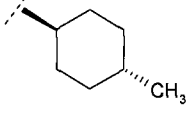
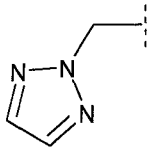
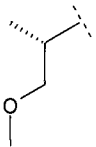
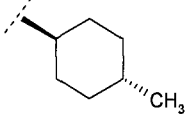
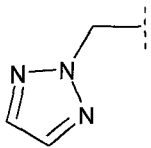
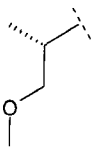
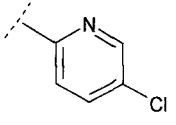
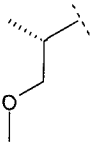
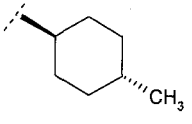
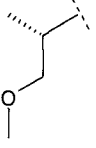
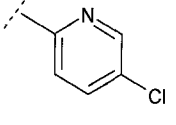
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1001	H	H			5.8	540	6A
1002	H	H			6.7	481.2	6A
1003	H	H			7.8	597.2	6A
1004	H	H			7.8	597.2	6A
1005	H	H			7.5	656	6A

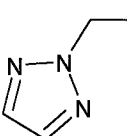
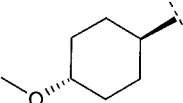
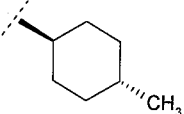
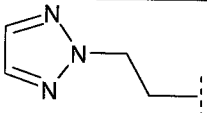
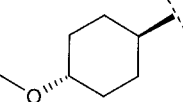
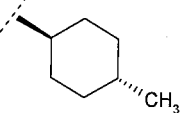
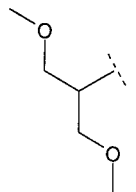
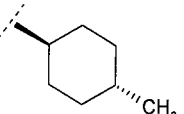
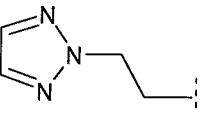
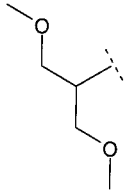
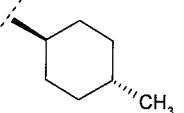
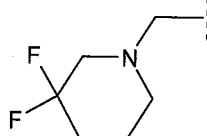
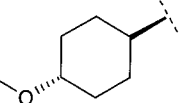
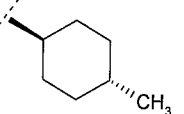
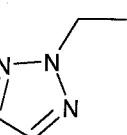
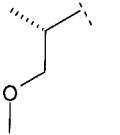
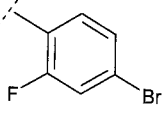
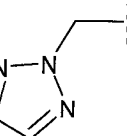
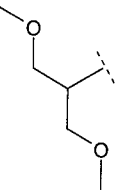
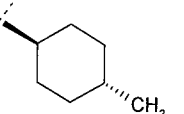
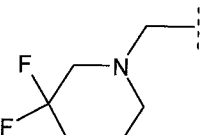
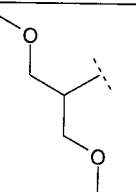
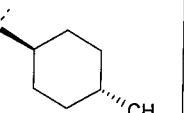
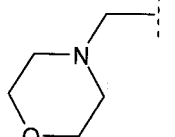
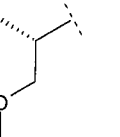
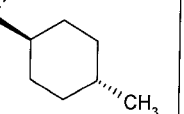
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1006	H	H			7.5	656.1	6A
1007		H			6.3	562.4	7A
1008		F			6.5	580.4	8A
1009		H			6.3	616.3	9A
1010		H			6.8	616.3	9A
1011	H	H			7.8	571.2	6A
1012	H	H			7.8	571.2	6A

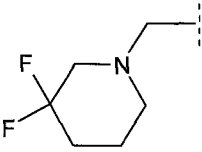
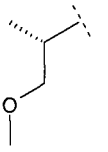
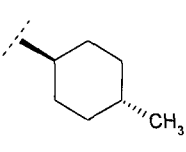
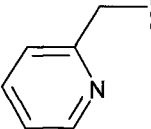
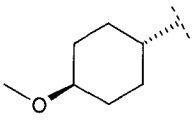
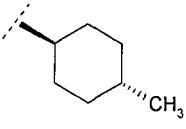
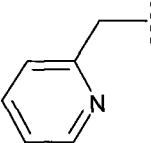
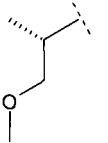
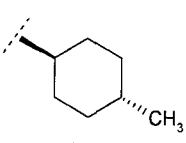
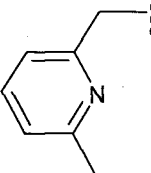
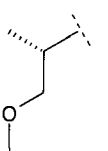
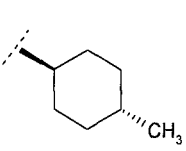
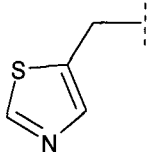
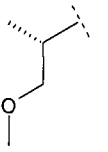
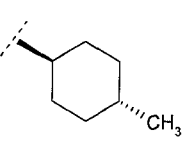
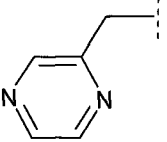
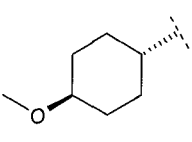
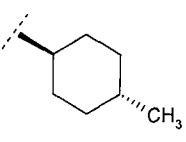
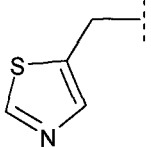
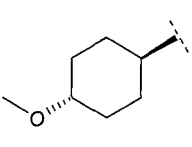
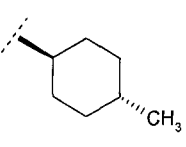
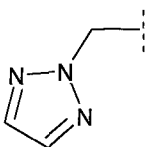
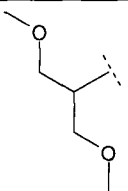
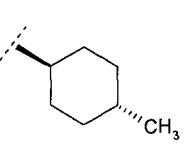
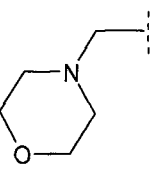
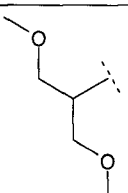
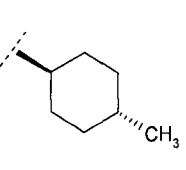
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1013	H	H			8.0	605.2	6A
1014	H	H			6.9	495.2	10A
1015	H	H			7.5	557.2	6A
1016	H	H			7.5	557.2	6A
1017	H	H			7.3	509.2	6A
1018	H	H			7.4	523.2	6A
1019	H	H			7.5	573.2	6A
1020	H	H			7.6	543.2	6A
1021	H	H			7.4	509.2	6A
1022	H	H			7.2	509.2	6A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1023	H	H			7.7	537.3	6A
1024	H	H			7.0	495.2	6A
1025	H	H			6.8	495.2	6A
1026	H	H			7.1	509.2	6A
1027	H	H			7.3	523.2	6A
1028	H	H			7.5	557.2	6A
1029	H	H			7.7	557.2	6A
1030	H	H			7.4	543.2	6A
1031	H	H			7.4	543.2	6A
1032	H	H			7.5	543.2	6A
1033	H	H			6.9	495.2	6A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1034	H	H			7.9	611.3	6A
1035	H	H			7.9	611.3	6A
1036	H	H			7.1	573.2	6A
1037	H	H			7.7	571.2	6A
1038	H	H			7.3	557.2	6A
1039	H	H			7.3	557.2	6A
1040	H	H			5.3	508.1	10A
1041	H	H			5.3	554.1	10A

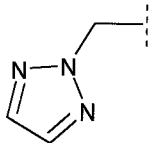
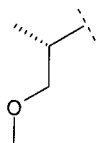
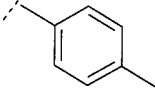
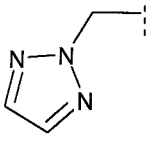
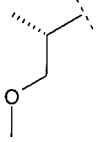
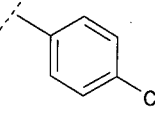
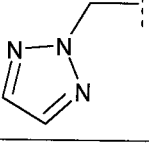
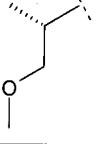
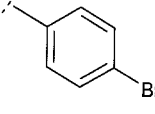
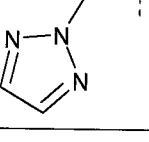
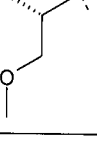
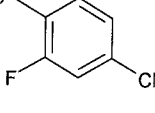
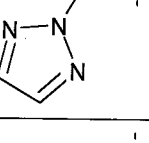
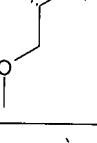
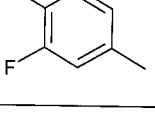
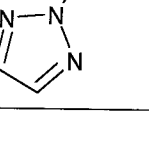
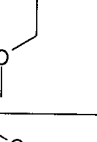
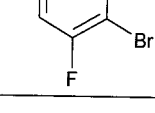
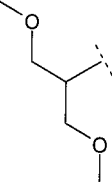
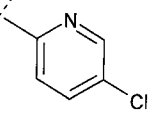
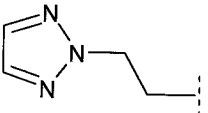
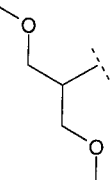
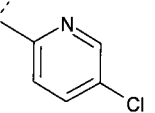
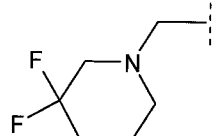
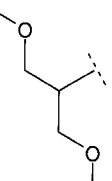
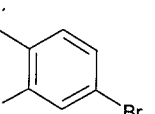
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1042	H	H			7.3	525.2	11A
1043		H			5.3	591.1	12A
1044		H			5.9	576.3	13A
1045		H			5.9	628.2	19A
1046		H			6.4	590.3	14A
1047		F			7.5	616.2	15A
1048		F			6.6	609.1	15A
1049	H	F			7.6	513.2	15A
1050	H	F			6.6	513.2	15A

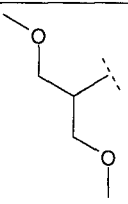
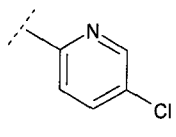
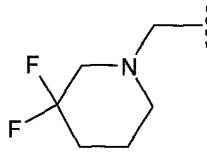
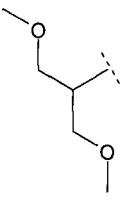
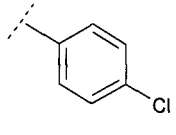
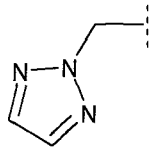
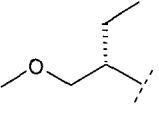
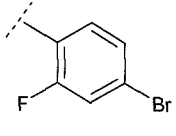
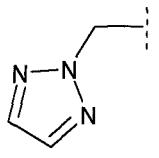
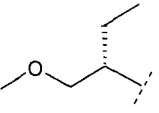
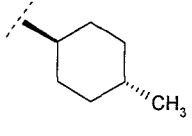
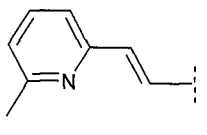
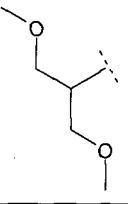
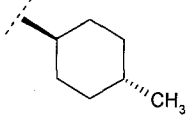
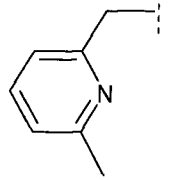
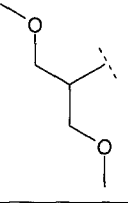
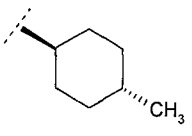
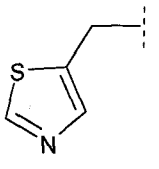
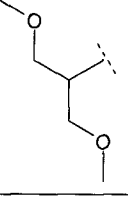
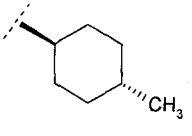
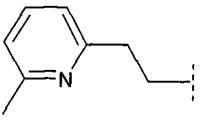
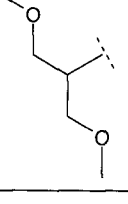
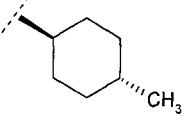
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1051		F			6.5	634.3	16A
1052		F			6.5	648.3	16A
1053	H	F			7.6	543.3	17A
1054		F			6.6	660.3	16A
1055		F				686.3	16A
1056		F			5.9	670.1	15A
1057		F			7.5	624.3	16A
1058		F			6.1	676.3	16A
1059		H			4.7	594.3	18A

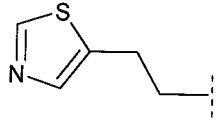
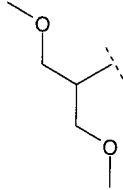
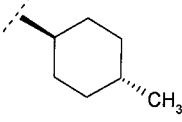
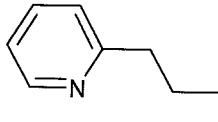
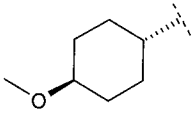
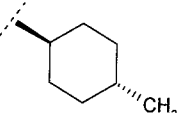
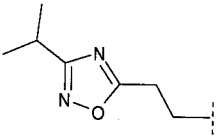
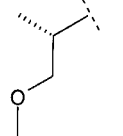
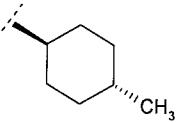
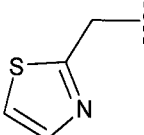
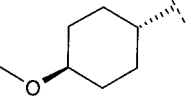
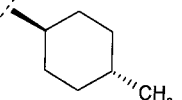
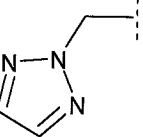
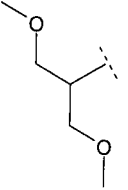
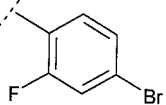
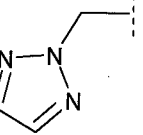
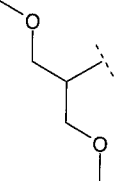
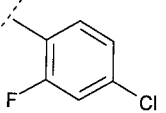
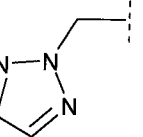
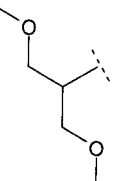
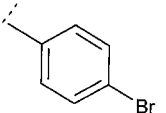
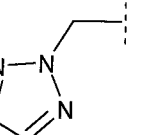
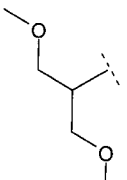
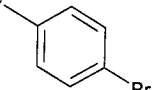
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1060		F				644.3	19A
1061		H			5.7	626.3	20A
1062		H			4.9	586.3	20A
1063		H			4.9	600.3	20A
1064		H			6.2	592.2	20A
1065		H			6.8	625.3	20A
1066		H			7.1	632.3	20A
1067		H			7.3	606.3	19A
1068		F			5.4	642.3	16A

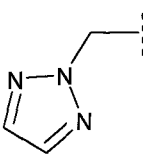
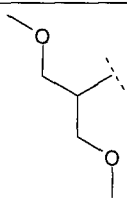
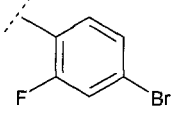
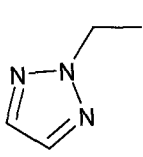
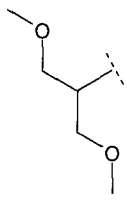
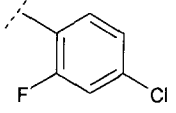
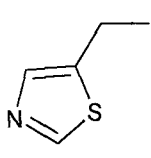
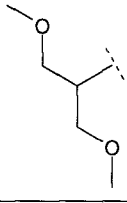
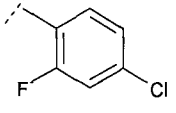
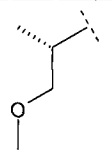
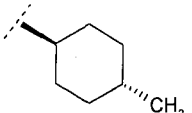
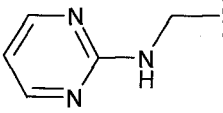
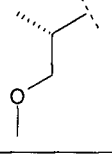
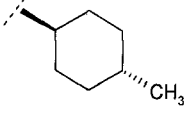
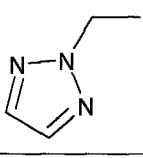
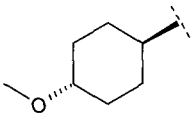
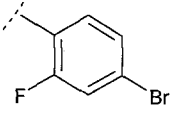
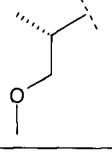
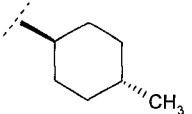
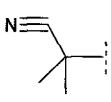
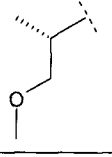
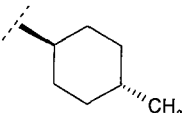
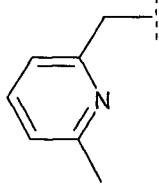
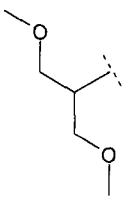
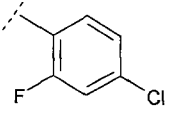
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1069		F			5.3	612.3	19A
1070		H			4.9	586.3	20A
1071		F			5.5	653.1	15A
1072		F			6.5	608.3	21A
1073		F			6.1	644.3	20A
1074		F			7.5	650.3	20A
1075		F			7.8	650.3	20A
1076		H			6.4	620.3	16A
1077		H			5.6	652.1	14A

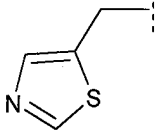
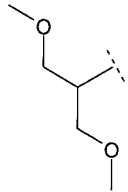
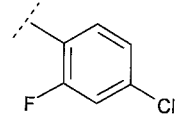
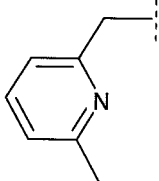
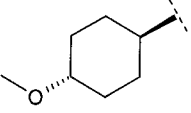
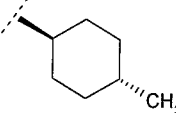
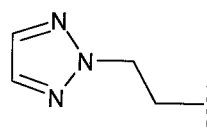
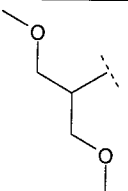
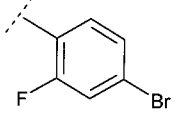
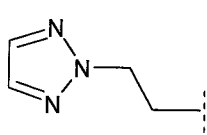
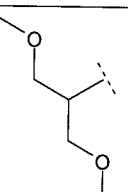
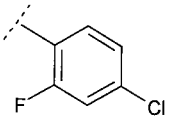
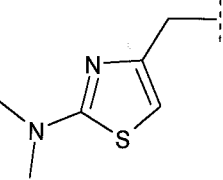
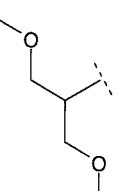
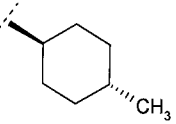
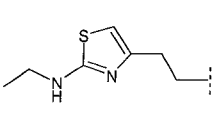
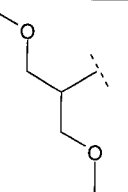
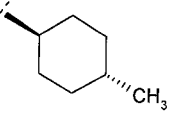
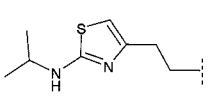
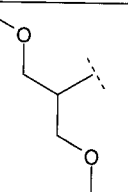
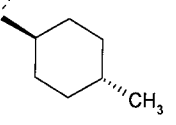
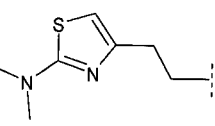
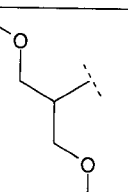
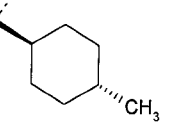
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1078		H			5.8	658.3	16A
1079		H			5.1	624.3	16A
1080		F			4.9	656.4	16A
1081		F			5.2	690.4	16A
1082	H	F			7.5	619.2	22A
1083		H			5.4	630.4	20A
1084		H			7.1	622.3	20A
1085		F			6.9	623.2	15A

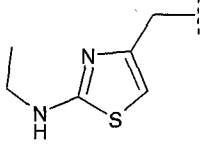
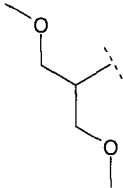
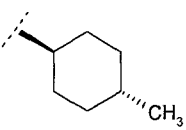
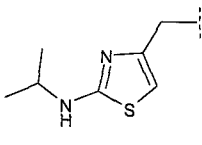
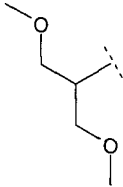
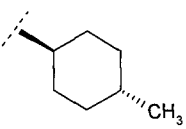
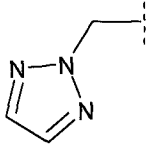
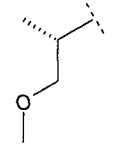
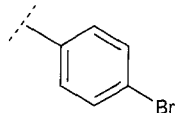
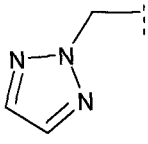
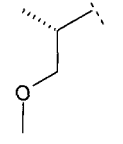
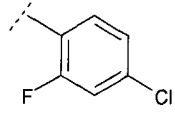
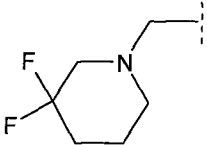
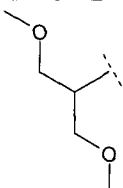
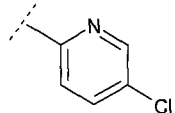
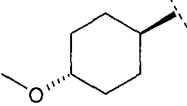
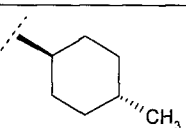
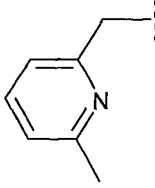
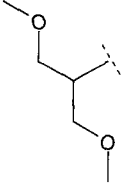
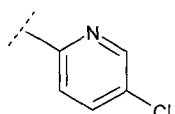
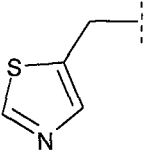
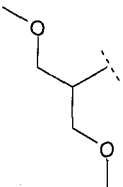
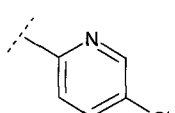
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1086		H			6.4	570.2	14A
1087		H			6.6	590.2	14A
1088		H			6.7	634.1	14A
1089		H			6.7	608.2	14A
1090		H			6.5	588.2	14A
1091		H			6.8	652.1	14A
1092		F			6.6	584.1	23A
1093		F			6.2	653.2	23A
1094		H			5.7	736.2	24A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1095	H	F			6.9	558.2	22A
1096		H			5.5	672.2	24A
1097		F			7.6	684.1	15A
1098		H			7.6	590.3	10A
1099		F			5.3	660.3	25A
1100		F			5.1	648.3	20A
1101		F			6.5	640.3	20A
1102		F			5.1	662.3	26A

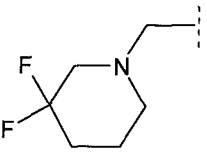
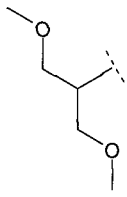
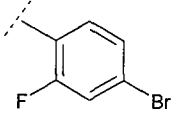
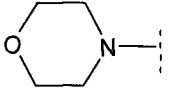
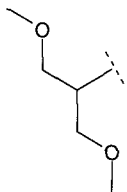
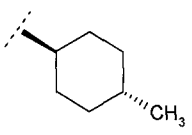
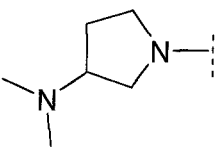
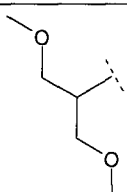
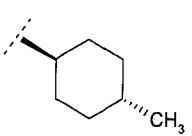
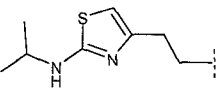
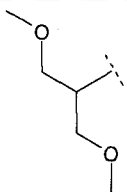
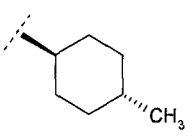
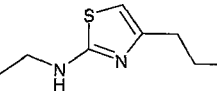
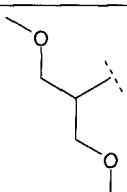
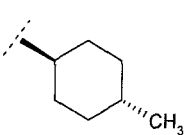
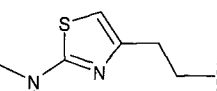
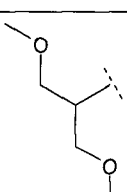
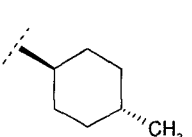
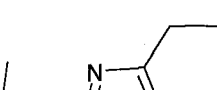
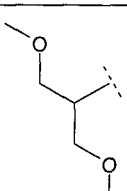
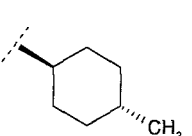
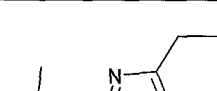
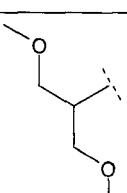
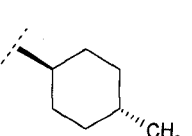
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1103		F			6.5	654.3	27A
1104		F			5.7	658.3	27A
1105		H			6.5	633.3	28A
1106		H			7.3	632.3	20A
1107		H			6.9	684.1	29A
1108		H			6.8	638.2	29A
1109		H			6.7	666.1	29A
1110		F			7.0	682.1	30A

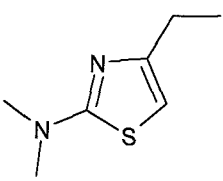
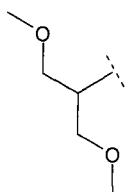
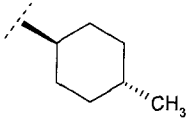
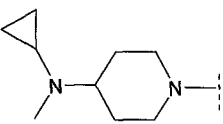
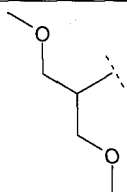
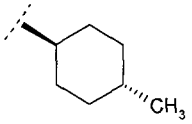
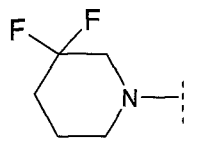
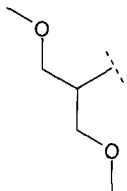
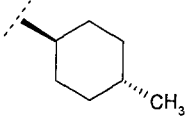
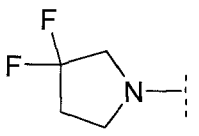
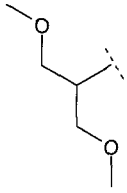
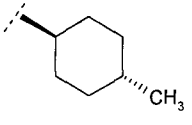
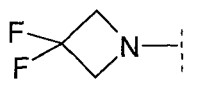
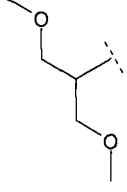
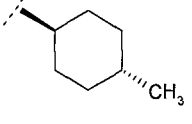
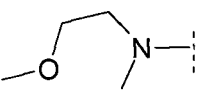
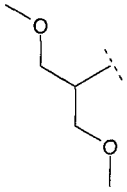
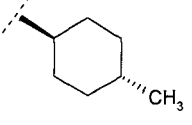
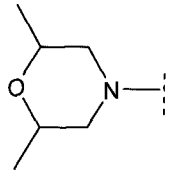
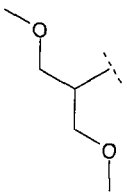
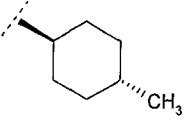
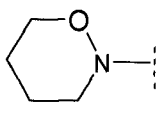
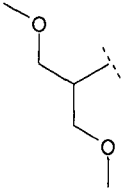
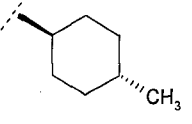
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1111		F			7.2	700.1	30A
1112		F			7.2	656.2	30A
1113		H			6.7	654.2	31A
1114		H			7.1	534.3	32A
1115		H			5.6	602.3	33A
1116		F			7.2	710.2	34A
1117		H			7.5	560.3	32A
1118		H			7.6	560.3	32A
1119		F			5.8	680.2	31A

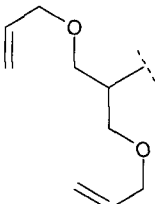
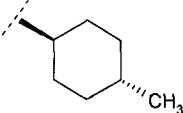
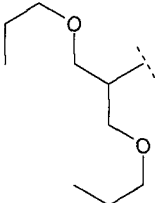
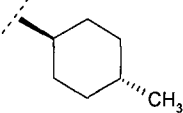
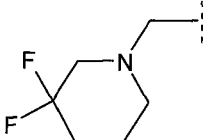
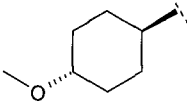
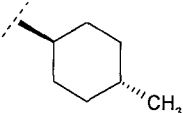
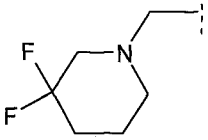
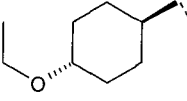
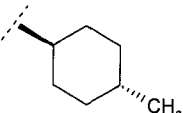
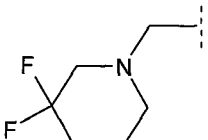
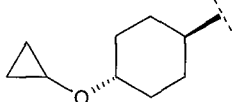
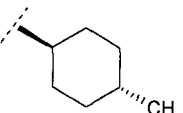
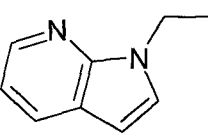
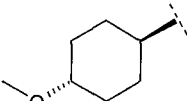
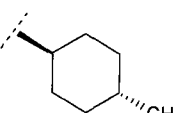
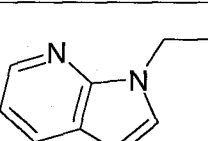
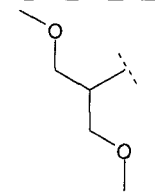
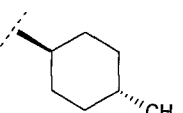
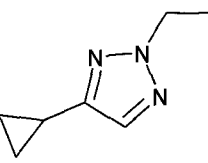
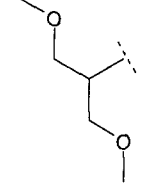
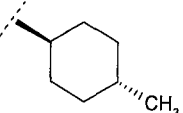
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1120		F			7.0	672.1	31A
1121		H			5.4	640.4	40A
1122		F			7.2	714.2	62A
1123		F			7.2	670.2	62A
1124		H			5.2	665.4	49A
1125		H			5.4	679.4	50A
1126		H			5.5	693.4	50A
1127		H			5.3	679.4	50A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1128		H			5.2	665.4	49A
1129		H			5.4	679.4	49A
1130		F			6.9	652.2	15A
1131		F			7.0	626.2	15A
1132		F			5.0	691.3	51B
1133	H	F			6.7	553.3	41A
1134		F			4.7	663.2	51C
1135		F			6.0	655.2	51C

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1136		H			6.9	698.2	63A
1137		H			6.8	652.2	63A
1138		H			6.7	680.2	63A
1139		H			7.3	610.3	42A
1140		H			5.4	673.4	42A
1141		H			5.5	677.3	42A
1142		F			5.9	690.1	64A
1143		F			5.9	734.1	64A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1144		F			6.0	752.1	64A
1145		F			7.7	628.3	42A
1146		F			5.5	655.4	42A
1147		F			5.6	711.3	52A
1148		F			5.5	697.3	52A
1149		F			5.4	697.3	52A
1150		F			5.4	683.3	53A
1151		F			5.6	697.3	53A

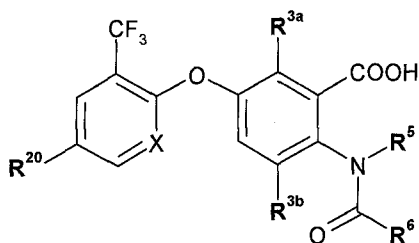
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1152		F			5.4	683.3	53A
1153		F			5.8	695.3	42A
1154		F			8.3	662.3	42A
1155		F			8.2	648.3	42A
1156		F			8.1	634.3	42A
1157		F			8.0	630.3	42A
1158		F			8.4	656.4	42A
1159		F			8.6	628.3	42A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1160	H	H			8.3	577.3	43A
1161	H	H			8.7	581.3	43A
1162		H			6.1	668.3	65A
1163		H			6.3	682.3	66A
1164		H			6.3	694.3	67A
1165		H			6.6	665.3	54A
1166		F			6.7	673.2	55A
1167		F			8.2	662.2 [M-H]	44B

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1168		F			6.7	683.3	56A
1169		F			6.4	674.3	68B
1170		F			7.8	638.2	45A
1171		F			7.5	615.2	81A
1172		F			8.4	627.2	69A
1173		F			8.0	664.2	69A
1174		F			7.2	664.2	69A
1175		F			6.8	638.2	74A

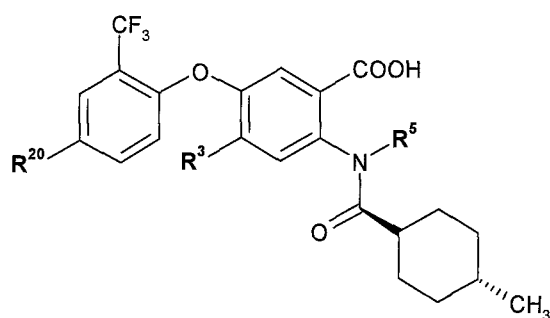
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
1176		F			8.1	674.3	44B
1177		F			7.7	648.2	45A
1178		F			7.9	662.2	45A
1179	H	H			7.3	529.2	6A

TABLE 2

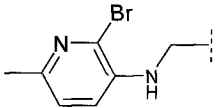
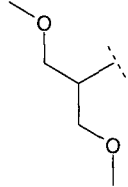
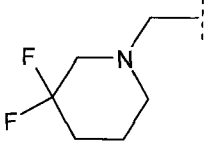
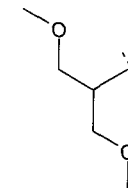
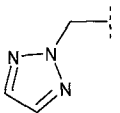
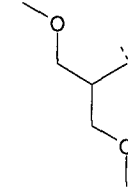
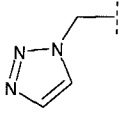
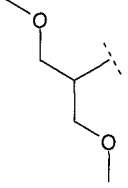
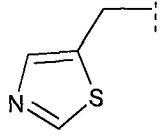
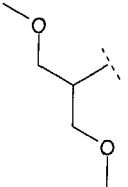
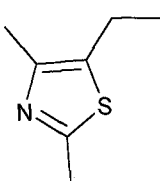
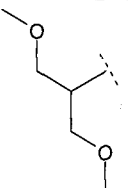
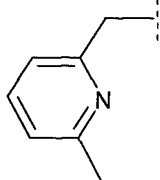
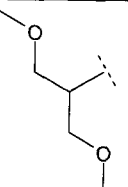
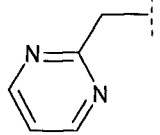
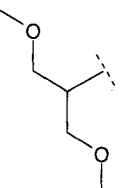


Cpd	R ²⁰	R ^{3a}	R ^{3b}	X	R ⁵	R ⁶	t _R (min)	MS (M+H) ⁺	Method
2001		H	F	N			7.6	594.3	35A
2002		F	H	N			7.3	594.3	36A
2003		Me	H	CH			7.8	619.2	70B

TABLE 3

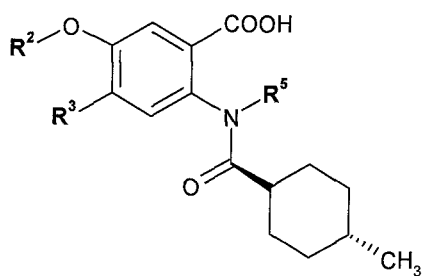


Cpd	R ²⁰	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
3001		H		5.2	657.4	37A
3002		H		6.4	621.3	38A
3003		H		5.0	629.3	38A
3004		H		6.3	616.3	38A
3005		H		6.4	605.3	39A
3006		H		6.1	605.3	39A

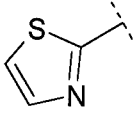
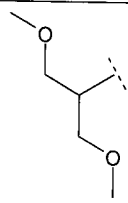
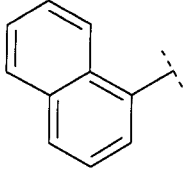
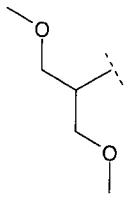
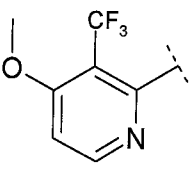
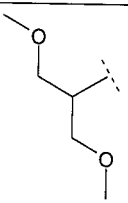
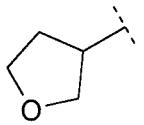
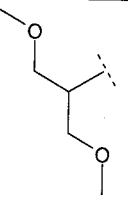
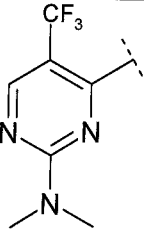
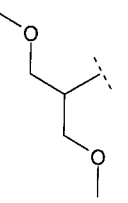
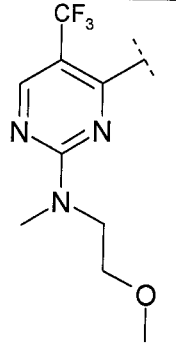
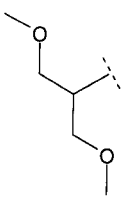
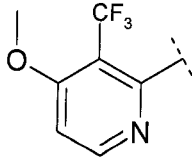
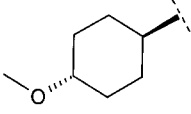
Cpd	R ²⁰	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
3007		F		6.9	740.2	59A
3008		F		5.5	675.4	57B
3009		F		6.6	623.3	57D
3010		F		6.3	623.3	57D
3011		F		6.5	639.3	58A
3012		F		6.1	667.3	58A
3013		F		5.5	647.2	58A
3014		F		6.5	634.2	58A

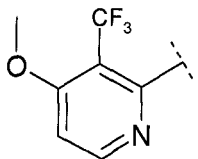
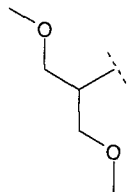
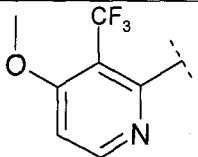
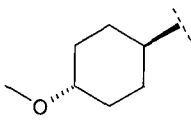
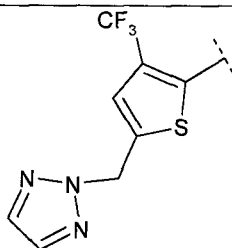
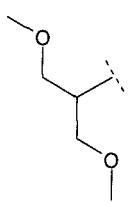
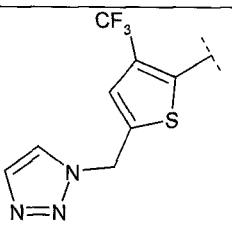
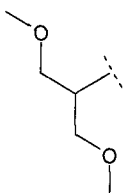
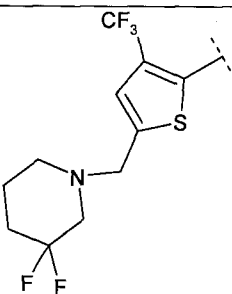
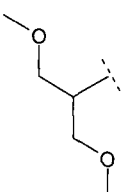
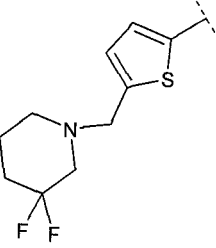
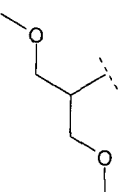
Cpd	R ²⁰	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
3015		F		6.8	666.2	59A

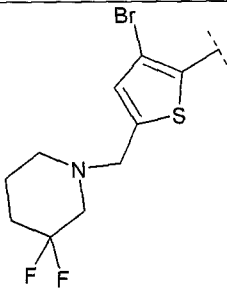
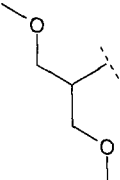
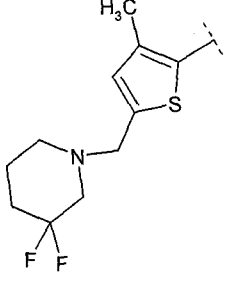
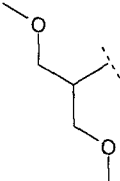
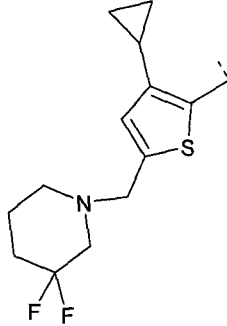
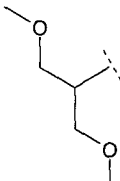
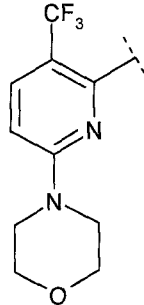
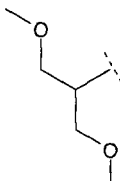
TABLE 4



Cpd	R ²	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
4001		F		7.9	574.3	46A
4002		H		7.7	507.3	71A
4003		H		7.5	507.3	72A
4004		H		6.1	504.3	60A

Cpd	R ²	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
4005		H		5.8	463.3	60A
4006		H		8.5	506.3	73A
4007		H		6.4	555.3	61B
4008		H		5.9	450.3	47A
4009		F		8.1	587.3	48A
4010		F		8.2	631.3	48A
4011		F		6.5	583.2	61B

Cpd	R ²	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
4012		F		6.6	573.2	61B
4013		H		6.4	565.2	61B
4014		H		6.5	611.2	79A
4015		H		6.1	611.2	79A
4016		H		5.6	663.2	75A
4017		H		4.9	595.2	76A

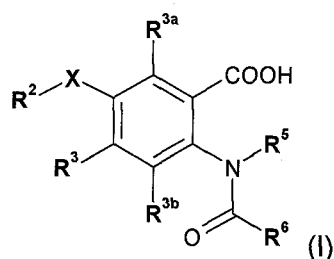
Cpd	R ²	R ³	R ⁵	t _R (min)	MS (M+H) ⁺	Synthetic Method
4018		H		5.6	673.1	77A
4019		H		5.0	609.2	78A
4020		H		5.3	635.2	78A
4021		F		8.3	628.3	48B

Each of the references, including all patents, patent applications and publications, listed in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

CLAIMS

1. An isomer, racemate, enantiomer or diastereomer of a compound of formula (I):

5



wherein:

X is selected from O and S;

- 10 R^2 is **Het** or aryl, optionally substituted with 1 to 5 R^{20} substituents, wherein R^{20} in each case is independently selected from:

a) halo, cyano or nitro;

b) R^7 , $-C(=O)-R^7$, $-C(=O)-O-R^7$, $-O-R^7$, $-S-R^7$, $-SO-R^7$, $-SO_2-R^7$,

$-(C_{1-6})alkylene-R^7$, $-(C_{1-6})alkylene-C(=O)-R^7$,

- 15 $-(C_{1-6})alkylene-C(=O)-O-R^7$, $-(C_{1-6})alkylene-O-R^7$, $-(C_{1-6})alkylene-S-R^7$, $-(C_{1-6})alkylene-SO-R^7$ or $-(C_{1-6})alkylene-SO_2-R^7$;

wherein R^7 is in each instance independently selected from H,

$(C_{1-6})alkyl$, $(C_{2-6})alkenyl$, $(C_{2-6})alkynyl$, $(C_{1-6})haloalkyl$, $(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-6})alkyl$, aryl and **Het**;

- 20 wherein the $(C_{1-6})alkyl$, $(C_{2-6})alkenyl$, $(C_{2-6})alkynyl$, $(C_{1-6})haloalkyl$, $(C_{3-7})cycloalkyl$, $(C_{3-7})cycloalkyl-(C_{1-6})alkyl$, and $(C_{1-6})alkylene$ are

optionally substituted with 1 or 2 substituents each independently

selected from $-OH$, $-(C_{1-6})alkyl$ (optionally substituted with

$-O-(C_{1-6})alkyl$), halo, $-(C_{1-6})haloalkyl$, $(C_{3-7})cycloalkyl$, $-O-(C_{1-6})alkyl$,

- 25 cyano, $COOH$, $-NH_2$, $-NH(C_{1-4})alkyl$, $-NH(C_{3-7})cycloalkyl$,

$-N((C_{1-4})alkyl)(C_{3-7})cycloalkyl$, $-N((C_{1-4})alkyl)_2$, aryl, $-(C_{1-6})alkyl-aryl$, **Het**,

$-(C_{1-6})alkyl-Het$; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

- 30 i) halo, cyano, oxo, thioxo, imino, $-OH$, $-O-(C_{1-6})alkyl$,

- O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,
 -C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 -C(=O)-NH(C₃₋₇)cycloalkyl,
 5 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
 ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
 -O-(C₁₋₆)alkyl; and
 10 iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
 substituted with halo or (C₁₋₆)alkyl; and
 c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹,
 -(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹,
 -(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹;
 15 wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2
 substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo,
 -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂,
 -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and
 -N((C₁₋₄)alkyl)₂;
 20 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
 (C₃₋₇)cycloalkyl; and
 R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl,
 -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and
 -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;
 25 or R⁸ and R⁹, together with the N to which they are attached,
 are linked to form a 4- to 7-membered heterocycle optionally further
 containing 1 to 3 heteroatoms each independently selected from N, O
 and S, wherein each S heteroatom may, independently and where
 possible, exist in an oxidized state such that it is further bonded to
 30 one or two oxygen atoms to form the groups SO or SO₂;
 wherein the heterocycle is optionally substituted with 1 to 3
 substituents each independently selected from (C₁₋₆)alkyl,
 (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl,
 (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂,
 35 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl

and -NHC(=O)-(C₁₋₆)alkyl;

R³, **R**^{3a} and **R**^{3b} are selected from H, halo, CN, (C₁₋₄)alkyl, -OH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl) and -N((C₁₋₄)alkyl)₂;

5 **R**⁵ is **R**⁵¹ mono-, di-, or tri-substituted with O-**R**⁵²,

wherein **R**⁵¹ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, each **R**⁵¹ being optionally substituted with (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; and

10 **R**⁵² is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, said aryl and **Het** being optionally substituted with (C₁₋₆)alkyl or O-(C₁₋₆)alkyl;

R⁶ is (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**; being optionally substituted with 1 to 5 substituents each independently selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and -N(**R**⁸)**R**⁹; wherein **R**⁸ and **R**⁹ are as defined above; and

15 **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

20 or a salt or ester thereof.

25

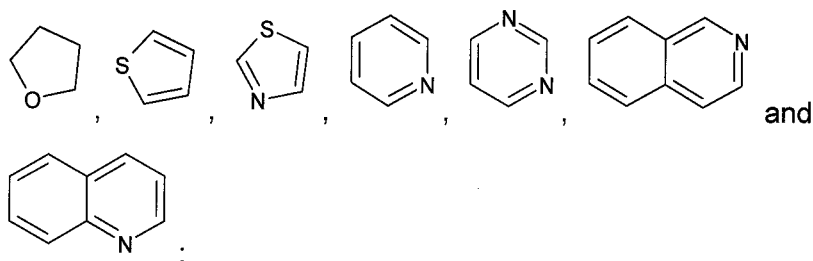
2. The compound according to claim 1, wherein **X** is O, and **R**², **R**³, **R**^{3a}, **R**^{3b}, **R**⁵, and **R**⁶ are as defined in claim 1.

30 3. The compound according to claim 1 or 2 wherein **R**² is aryl, optionally substituted with 1 to 5 **R**²⁰ substituents, and **R**²⁰ is as defined in claim 1.

4. The compound according to claim 1 or 2, wherein **R**² is phenyl or **Het** each being optionally substituted with 1 to 3 **R**²⁰ substituents, wherein **R**²⁰ is as defined in

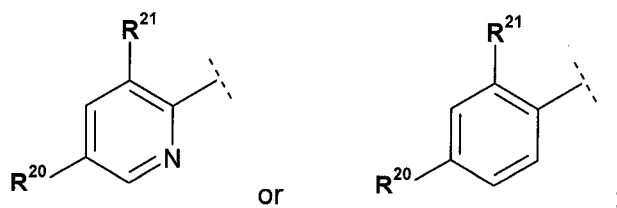
claim 1; and **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms.

- 5 **5.** The compound according to claim 1 or 2, wherein R^2 is **Het**; and **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms; wherein **Het** is optionally substituted with 1 to 3 R^{20} substituents, and R^{20} is as defined in claim 1.
- 10 **6.** The compound according to claim 5, wherein R^2 is **Het** selected from the group consisting of:



and wherein **Het** is optionally substituted with 1 to 3 R^{20} substituents as defined in claim 1.

- 7.** The compound according to claim 4 wherein R^2 is of the formula:



- 20 R^{21} is selected from H, halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl and $-O-(C_{1-6})$ haloalkyl; and R^{20} is as defined in claim 1.

- 8.** The compound of any one of claims 1 to 7 wherein R^{20} is selected from:

b) R^7 , $-(C_{1-6})$ alkylene- R^7 , $-(C_{1-6})$ alkylene-O- R^7 , $-(C_{1-6})$ alkylene-S- R^7 ;

25 wherein R^7 is in each instance independently selected from H, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyl- (C_{1-6}) alkyl, aryl and **Het**;

wherein the (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, and (C₁₋₆)alkylene are optionally substituted with 1 or 2 substituents each independently selected from -OH, -(C₁₋₆)alkyl optionally substituted with -O-(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂, **Het**, -(C₁₋₆)alkyl-**Het**; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

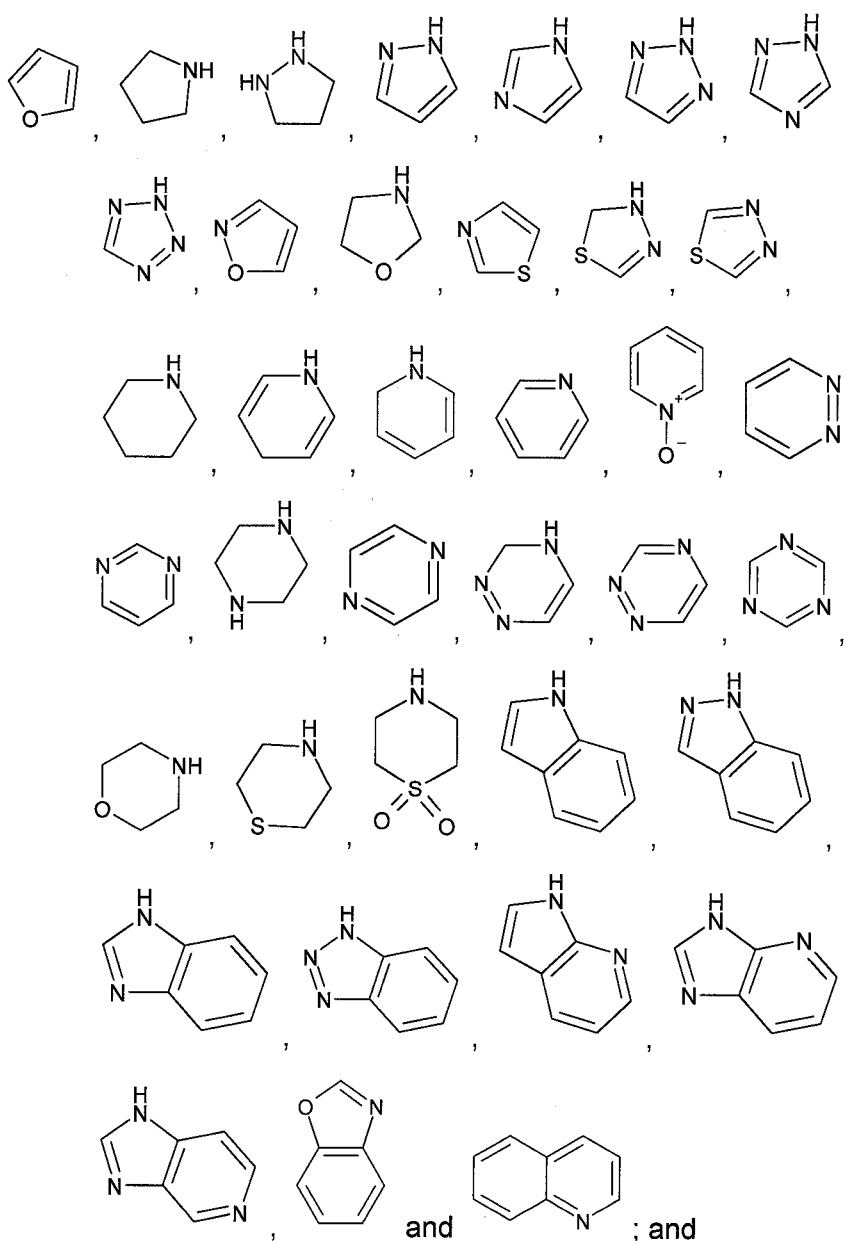
- 10 i) halo, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 -C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 15 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
 ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
 -O-(C₁₋₆)alkyl; and
 iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
 substituted with halo or (C₁₋₆)alkyl; and
 20 c) -N(R⁸)R⁹ or -(C₁₋₆)alkylene-N(R⁸)R⁹; wherein the (C₁₋₆)alkylene is
 optionally substituted with 1 or 2 substituents each independently
 selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl,
 -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;
 25 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
 (C₃₋₇)cycloalkyl; and
 R⁹ is defined as R⁷, wherein R⁷ is as defined above.

9. The compound according to any one of claims 1 to 7 wherein R²⁰ is selected
 30 from:

- b) R⁷ or -(C₁₋₆)alkylene-R⁷
 wherein R⁷ is in each instance independently selected from H,
 (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, phenyl and **Het**;
 wherein each of the phenyl and **Het** are optionally substituted with 1
 35 to 3 substituents each independently selected from:

- i) halo, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 -C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl; and
 ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or
 -O-(C₁₋₆)alkyl;

wherein the **Het** is selected from:



- c) -N(R⁸)R⁹ or -(C₁₋₆)alkylene-N(R⁸)R⁹;

R^8 is in each instance independently selected from H, (C_{1-6}) alkyl and (C_{3-7}) cycloalkyl; and

R^9 is defined as R^7 , wherein R^7 is as defined above.

- 5 **10.** The compound according to any one of claims 1 to 7 wherein R^{20} is selected from:

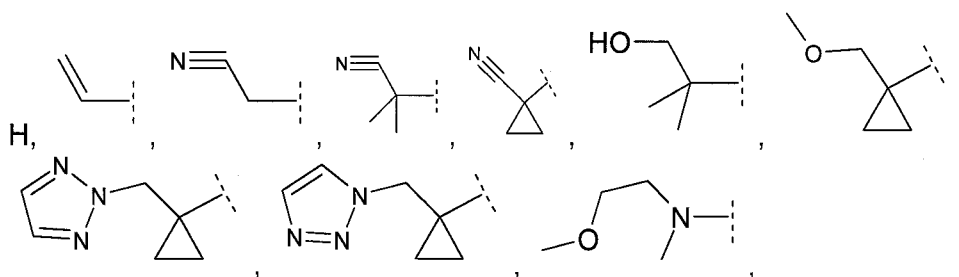
b) $-(C_{1-3})$ alkylene- R^7 ;

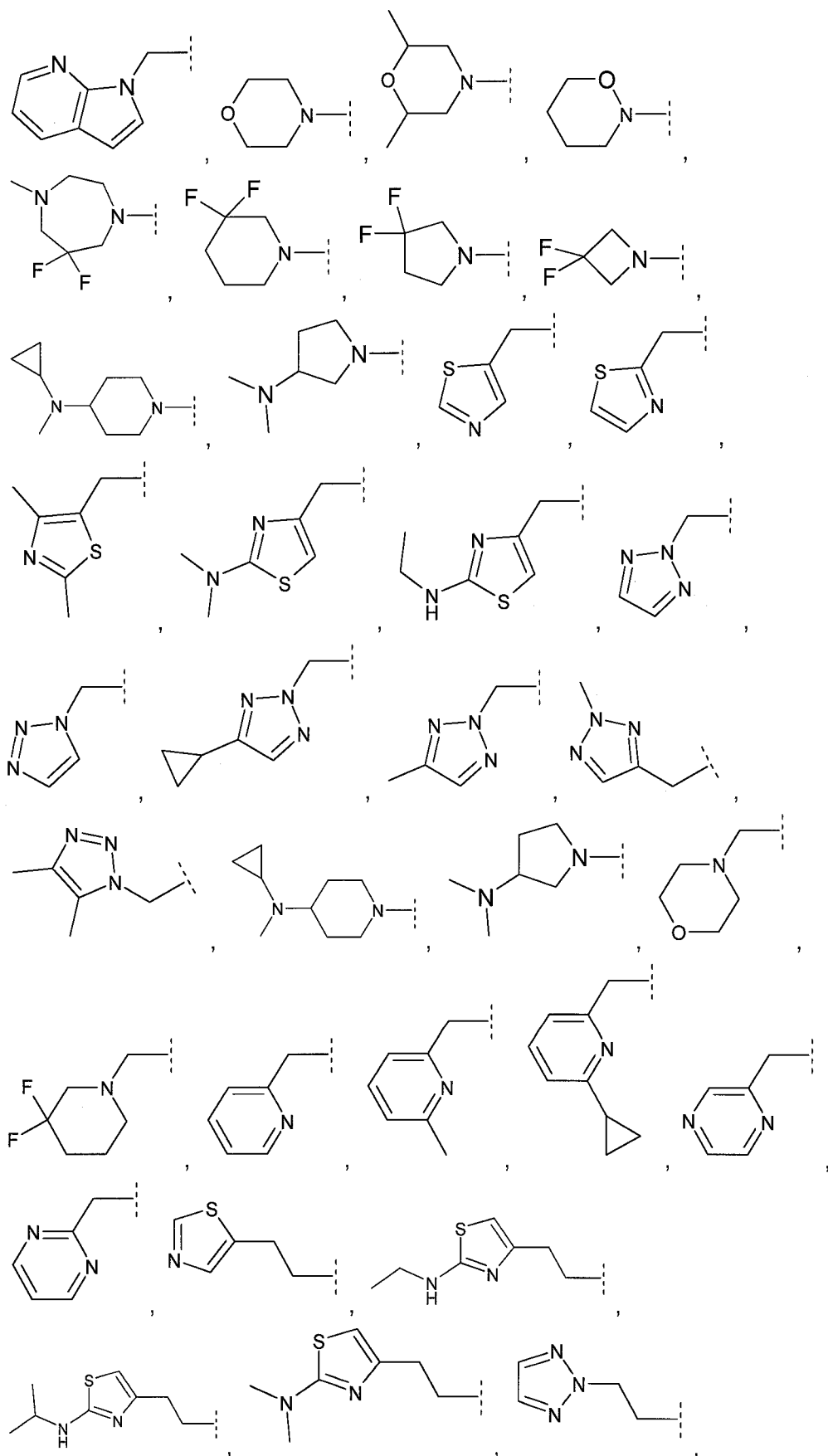
10 wherein R^7 is **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2 ;

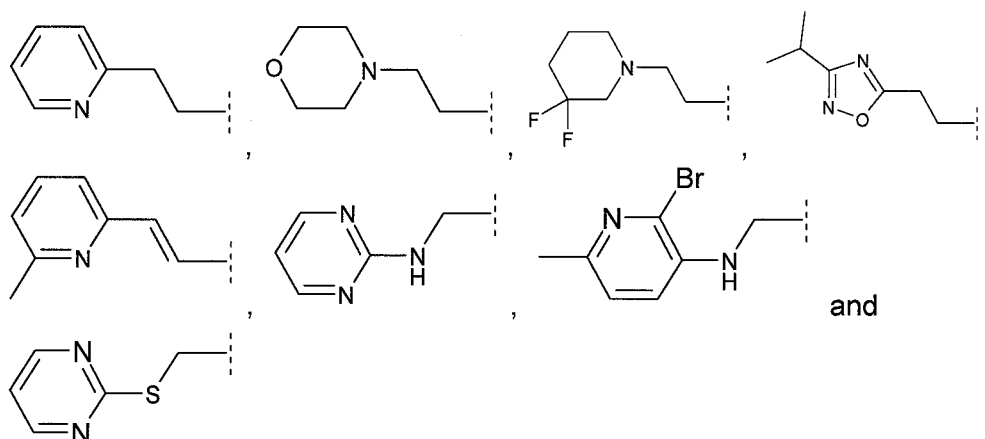
15 wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O- (C_{1-6}) alkyl, -O- (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl, $-NH_2$, $-NH(C_{1-4})$ alkyl, $-NH(C_{3-7})$ cycloalkyl, $-N((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl, $-N((C_{1-4})$ alkyl) $_2$, $-NH-C(=O)(C_{1-4})$ alkyl, (C_{1-6}) alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S.

25

- 11.** The compound according to any one of claims 1 to 7 wherein R^{20} is selected from:







5

12. The compound according to claim 7, wherein R^{21} is H or CF_3 , and R^{20} is as defined in any one of claims 8, 9, 10 or 11.

13. The compound according to any one of claims 1 to 12, wherein R^3 is selected from H, halo, CN, (C_{1-4}) alkyl, $-O-(C_{1-4})$ alkyl and $-N((C_{1-4})alkyl)_2$.

14. The compound according to claim 13, wherein R^3 is selected from H, F, Cl and CH_3 .

15. The compound according to any one of claims 1 to 14, wherein R^{3a} is selected from H, halo, (C_{1-4}) alkyl and CN.

16. The compound according to claim 15, wherein R^{3a} is selected from H, F and CH_3 .

20

17. The compound according to any one of claims 1 to 16, wherein R^{3b} is selected from H, halo, CN, (C_{1-4}) alkyl, $-O-(C_{1-4})$ alkyl and $-N((C_{1-4})alkyl)_2$.

18. The compound according to claim 17, wherein R^{3b} is selected from H, F, Cl, CH_3 and CN.

25

19. The compound according to any one of claims 1 to 18, wherein R^5 is R^{51} mono-, di-, or tri-substituted with $O-R^{52}$, wherein R^{51} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl,

(C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, each R⁵¹ being optionally substituted with (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; and R⁵² is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**, said aryl and **Het** being optionally substituted with (C₁₋₆)alkyl or O-(C₁₋₆)alkyl.

20. The compound according to claim 19, wherein R⁵ is R⁵¹ being mono- or di-substituted with O-R⁵², wherein R⁵¹ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, each R⁵¹ being optionally substituted with (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; and R⁵² is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl or (C₁₋₆)alkyl-aryl, said aryl being optionally substituted with (C₁₋₆)alkyl or O-(C₁₋₆)alkyl.

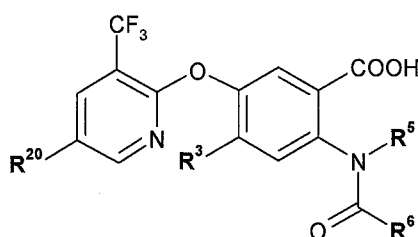
21. The compound according to any one of claims 1 to 20, wherein R⁶ is (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, (C₁₋₆)alkyl-aryl, **Het** or (C₁₋₆)alkyl-**Het**; being optionally substituted with 1 to 5 substituents each independently selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and -N(R⁸)R⁹; wherein R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above; or R⁸ and R⁹, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂; wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl.

22. The compound according to claim 21, wherein R⁶ is (C₅₋₆)cycloalkyl, phenyl or

Het optionally substituted with 1 to 3 substituents each independently selected from halo, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl; wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 nitrogen heteroatoms.

- 5 **23.** The compound according to claim 21, wherein **R**⁶ is phenyl, cyclohexyl or pyridine optionally substituted with 1 to 3 substituents each independently selected from halo, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl.

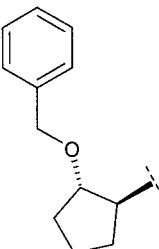
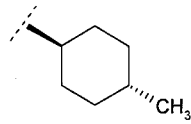
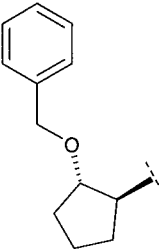
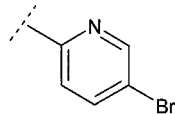
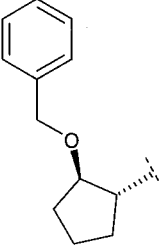
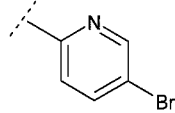
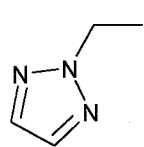
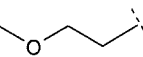
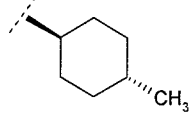
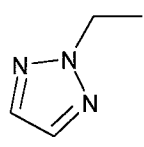
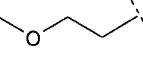
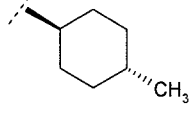
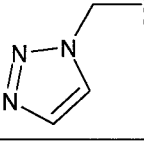
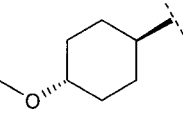
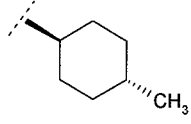
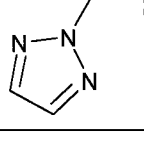
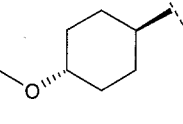
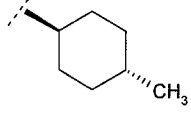
- 24.** The compound according to claim 1 having the following formula:

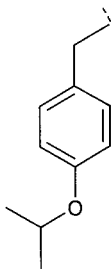
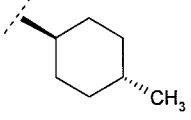
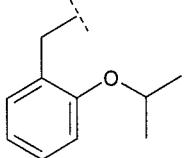
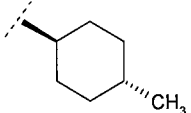
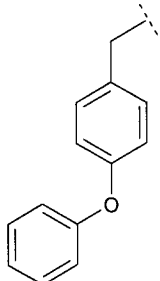
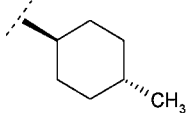
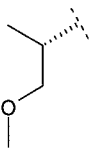
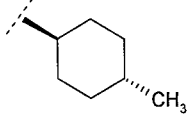
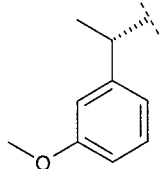
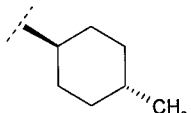
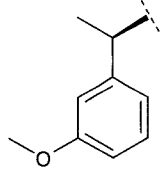
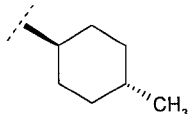
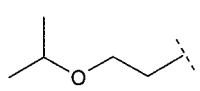
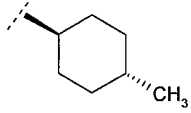
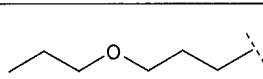
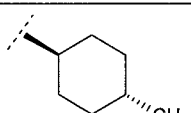
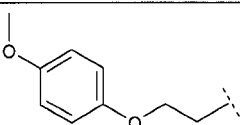
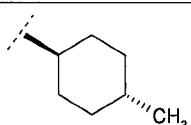


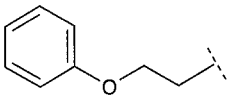
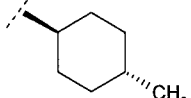
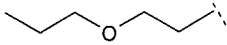
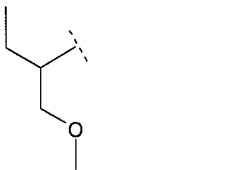
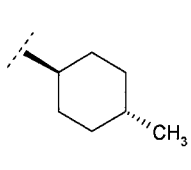
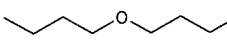
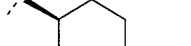
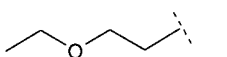
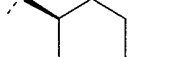
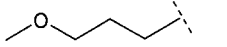
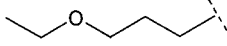
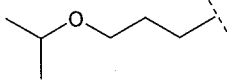
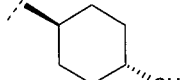
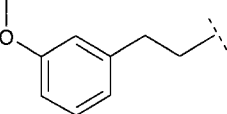
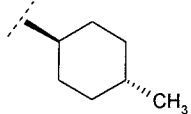
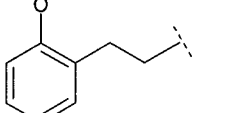
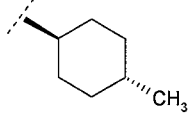
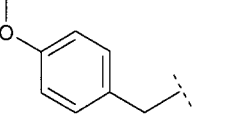
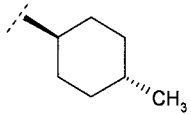
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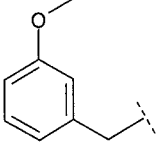
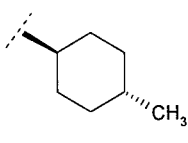
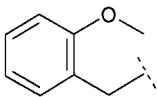
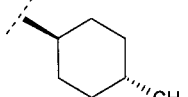
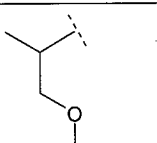
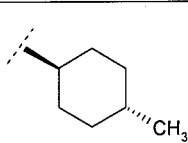
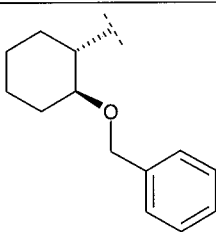
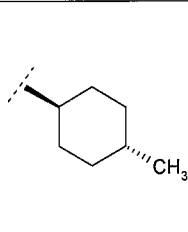
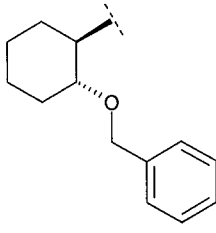
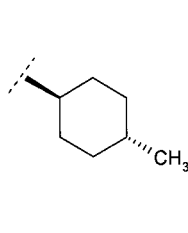
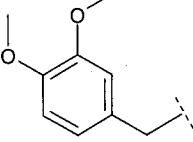
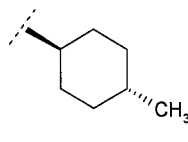
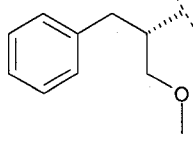
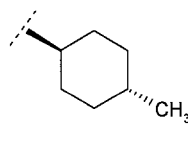
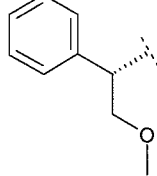
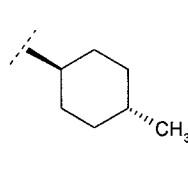
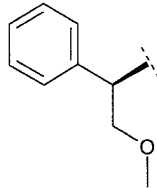
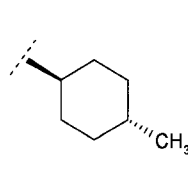
wherein **R**²⁰, **R**³, **R**⁵ and **R**⁶ are defined as:

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1001	H	H		
1002	H	H		
1003	H	H		

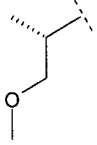
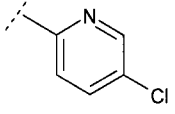
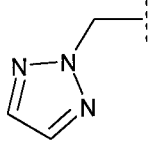
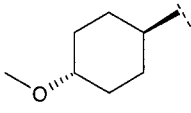
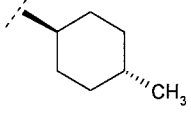
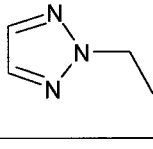
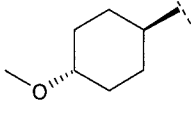
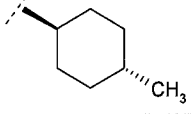
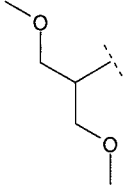
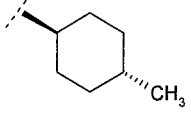
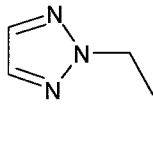
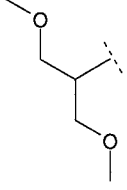
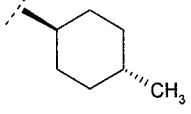
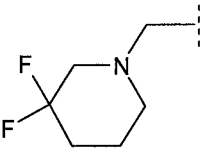
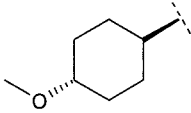
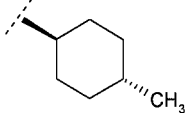
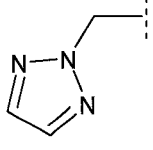
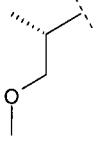
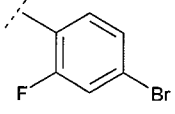
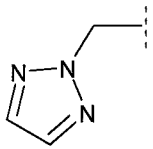
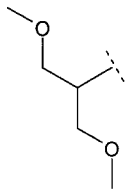
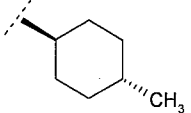
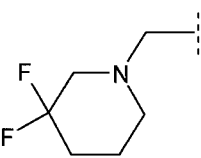
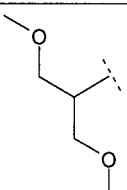
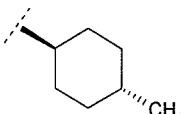
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1004	H	H		
1005	H	H		
1006	H	H		
1007		H		
1008		F		
1009		H		
1010		H		

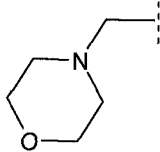
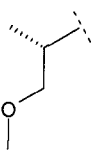
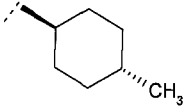
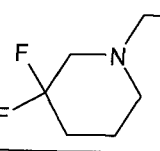
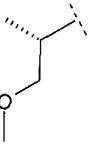
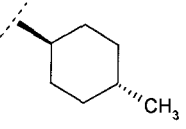
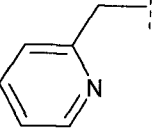
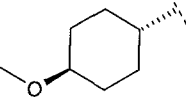
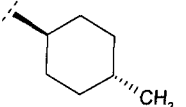
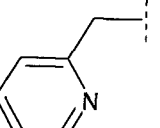
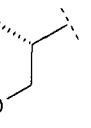
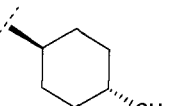
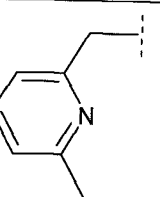
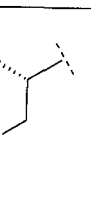
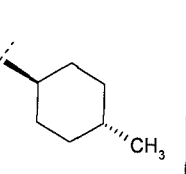
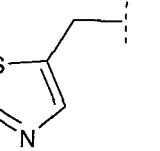
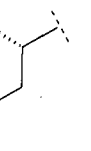
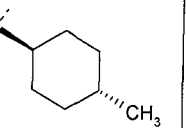
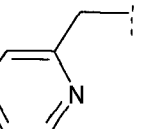
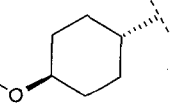
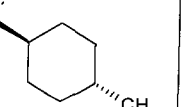
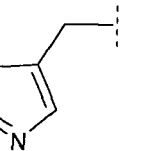
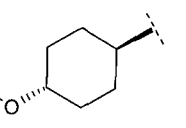
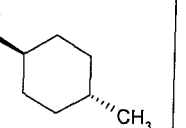
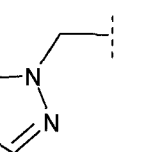
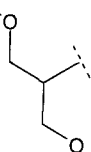
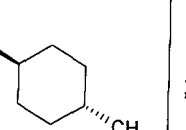
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1011	H	H		
1012	H	H		
1013	H	H		
1014	H	H		
1015	H	H		
1016	H	H		
1017	H	H		
1018	H	H		
1019	H	H		

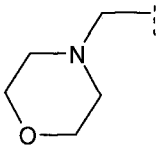
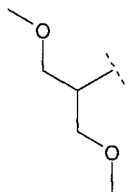
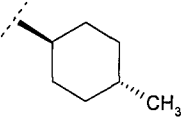
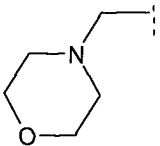
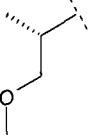
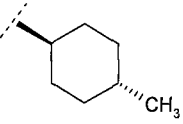
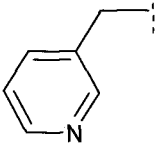
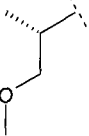
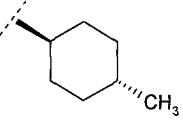
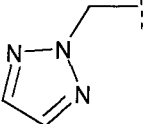
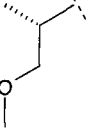
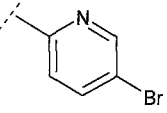
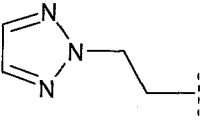
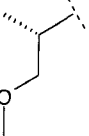
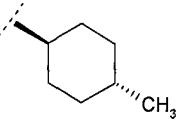
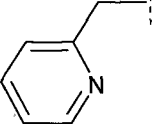
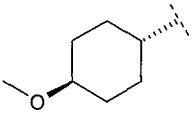
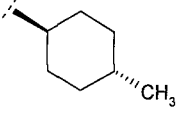
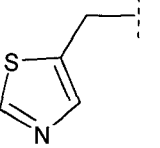
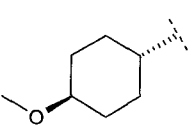
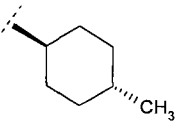
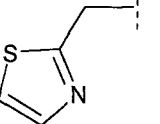
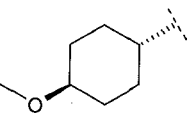
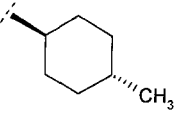
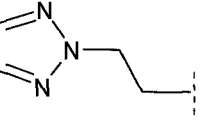
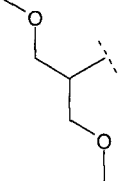
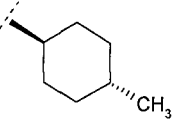
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1020	H	H		
1021	H	H		
1022	H	H		
1023	H	H		
1024	H	H		
1025	H	H		
1026	H	H		
1027	H	H		
1028	H	H		
1029	H	H		
1030	H	H		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1031	H	H		
1032	H	H		
1033	H	H		
1034	H	H		
1035	H	H		
1036	H	H		
1037	H	H		
1038	H	H		
1039	H	H		

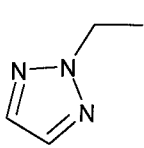
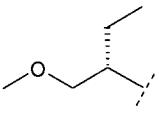
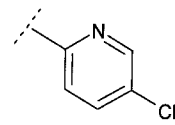
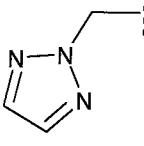
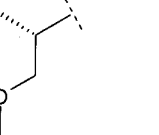
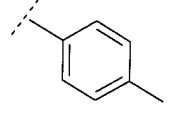
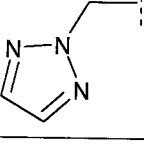
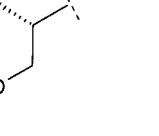
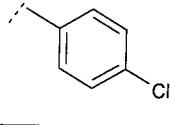
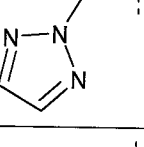
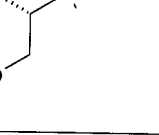
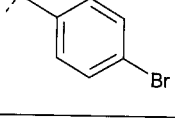
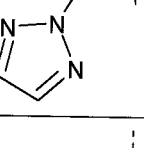
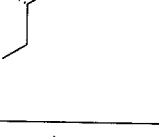
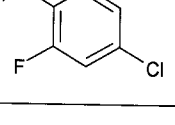
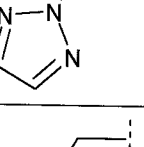
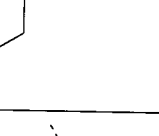
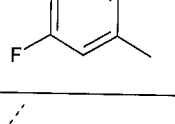
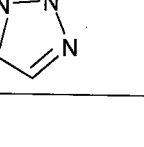
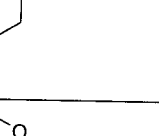
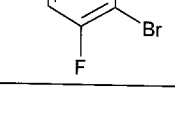
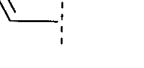
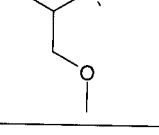
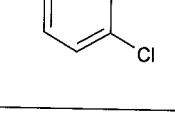
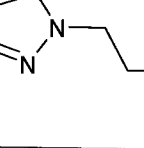
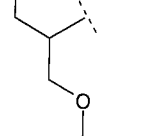
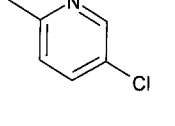
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1040	H	H		
1041	H	H		
1042	H	H		
1043		H		
1044		H		
1045		H		
1046		H		
1047		F		
1048		F		
1049	H	F		

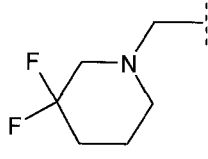
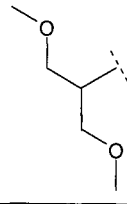
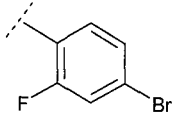
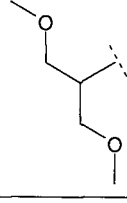
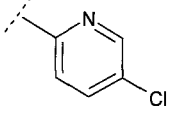
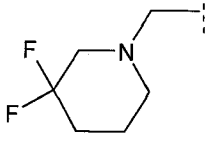
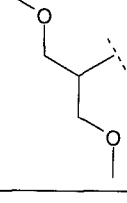
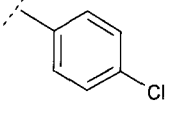
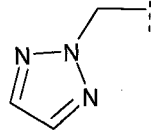
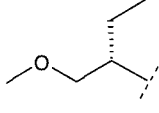
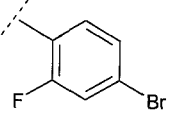
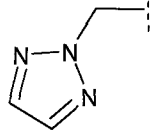
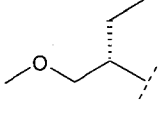
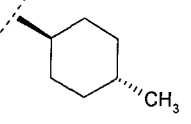
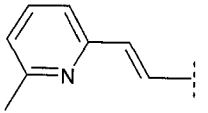
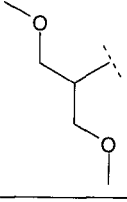
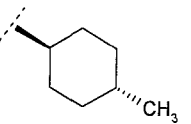
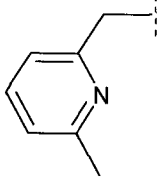
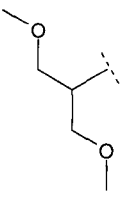
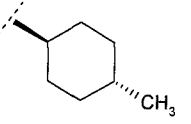
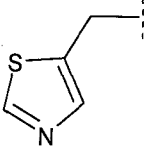
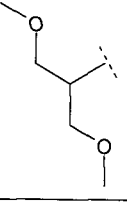
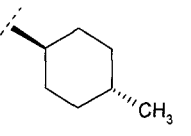
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1050	H	F		
1051		F		
1052		F		
1053	H	F		
1054		F		
1055		F		
1056		F		
1057		F		
1058		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1059		H		
1060		F		
1061		H		
1062		H		
1063		H		
1064		H		
1065		H		
1066		H		
1067		H		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1068		F		
1069		F		
1070		H		
1071		F		
1072		F		
1073		F		
1074		F		
1075		F		
1076		H		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1077		H		
1078		H		
1079		H		
1080		F		
1081		F		
1082	H	F		
1083		H		
1084		H		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1085		F		
1086		H		
1087		H		
1088		H		
1089		H		
1090		H		
1091		H		
1092		F		
1093		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1094		H		
1095	H	F		
1096		H		
1097		F		
1098		H		
1099		F		
1100		F		
1101		F		

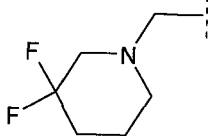
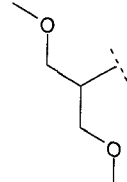
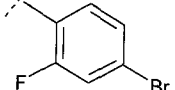
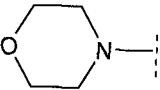
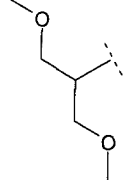
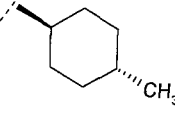
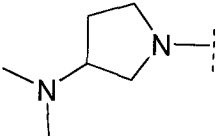
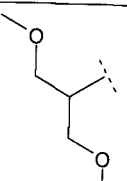
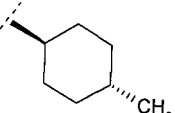
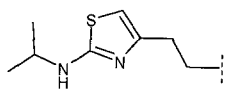
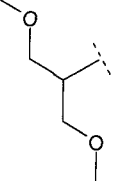
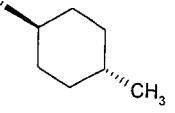
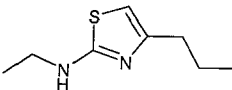
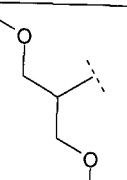
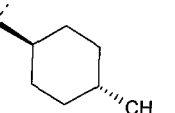
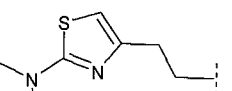
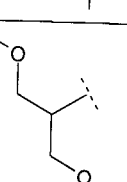
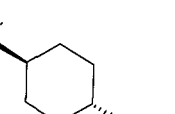
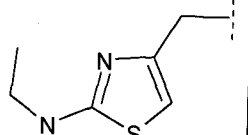
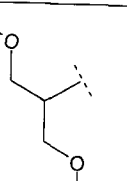
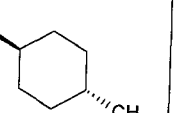
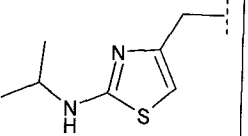
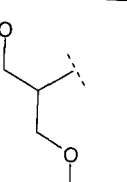
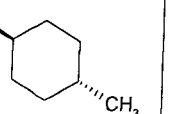
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1102		F		
1103		F		
1104		F		
1105		H		
1106		H		
1107		H		
1108		H		
1109		H		

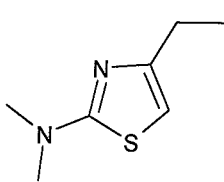
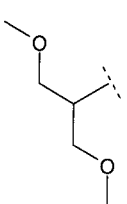
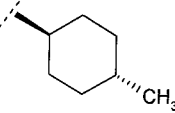
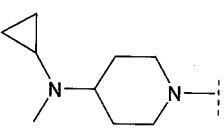
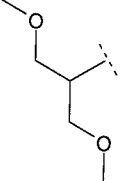
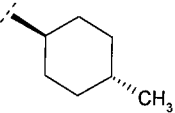
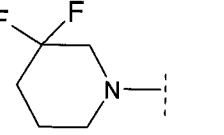
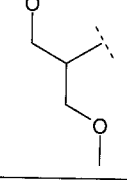
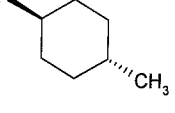
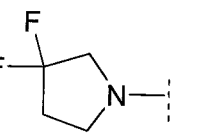
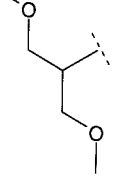
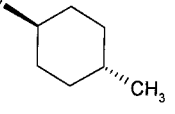
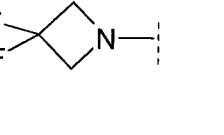
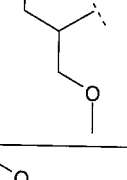
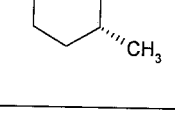
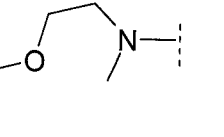
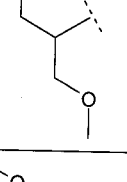
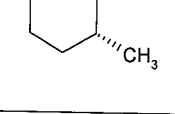
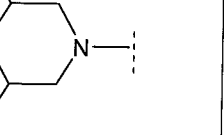
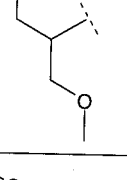
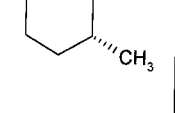
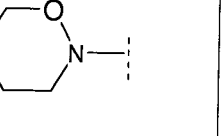
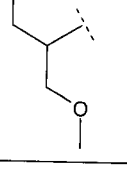
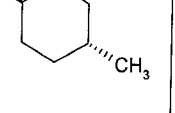
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1110		F		
1111		F		
1112		F		
1113		H		
1114		H		
1115		H		
1116		F		
1117		H		
1118		H		

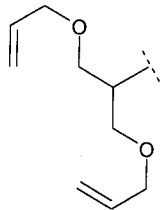
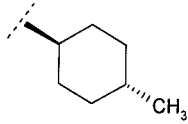
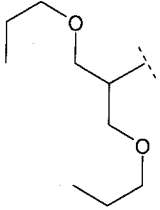
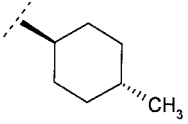
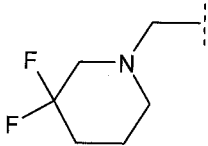
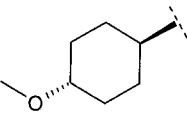
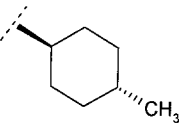
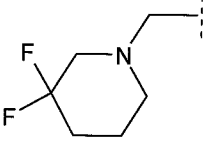
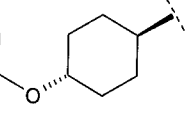
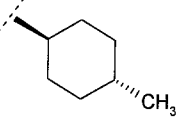
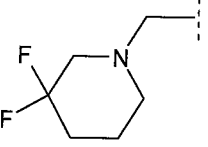
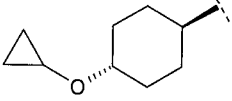
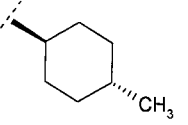
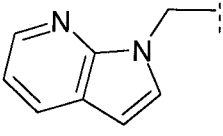
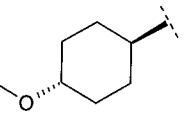
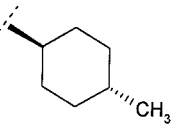
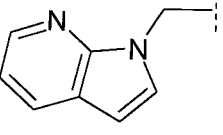
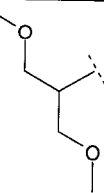
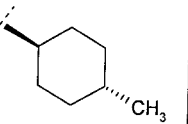
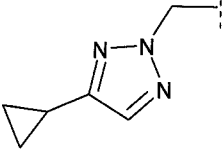
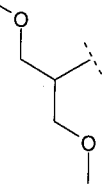
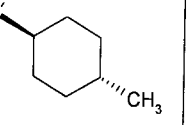
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1119		F		
1120		F		
1121		H		
1122		F		
1123		F		
1124		H		
1125		H		
1126		H		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1127		H		
1128		H		
1129		H		
1130		F		
1131		F		
1132		F		
1133	H	F		
1134		F		
1135		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1136		H		
1137		H		
1138		H		
1139		H		
1140		H		
1141		H		
1142		F		
1143		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1144		F		
1145		F		
1146		F		
1147		F		
1148		F		
1149		F		
1150		F		
1151		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1152		F		
1153		F		
1154		F		
1155		F		
1156		F		
1157		F		
1158		F		
1159		F		

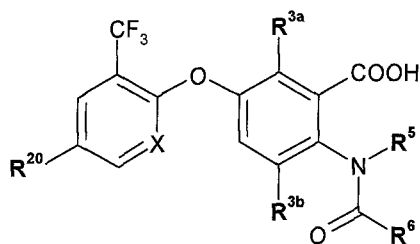
Cpd	R ²⁰	R ³	R ⁵	R ⁶
1160	H	H		
1161	H	H		
1162		H		
1163		H		
1164		H		
1165		H		
1166		F		
1167		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶
1168		F		
1169		F		
1170		F		
1171		F		
1172		F		
1173		F		
1174		F		
1175		F		

Cpd	R ²⁰	R ³	R ⁵	R ⁶	
1176		F			and
1177		F			
1178		F			
1179	H	H			

pharmaceutically acceptable salts or esters thereof.

25. A compound according to claim 1 having the following formula:



5

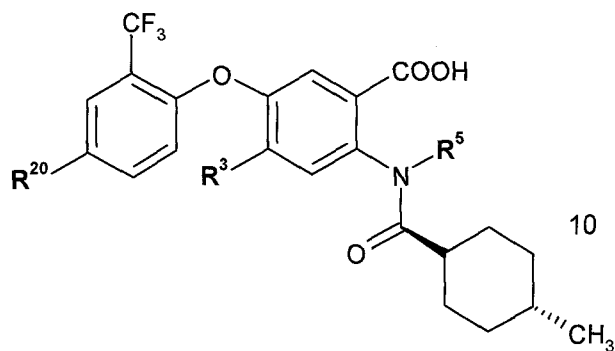
wherein R²⁰, R^{3a}, R^{3b}, X, R⁵ and R⁶ are defined as

Cpd	R ²⁰	R ^{3a}	R ^{3b}	X	R ⁵	R ⁶	
2001		H	F	N			and
2002		F	H	N			
2003		Me	H	CH			

pharmaceutically acceptable salts or esters thereof.

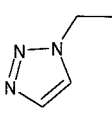
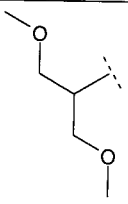
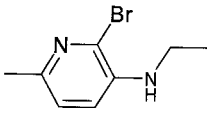
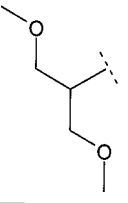
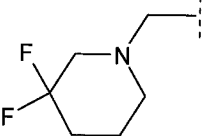
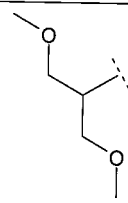
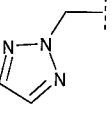
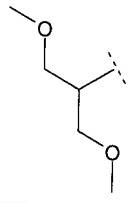
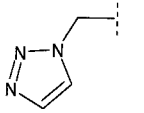
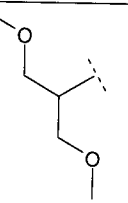
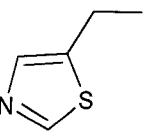
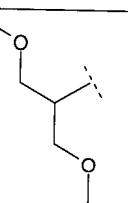
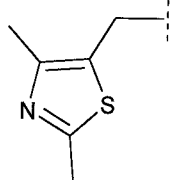
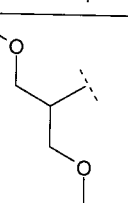
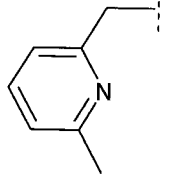
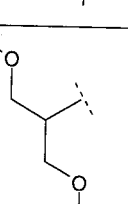
26. The compound according to claim 1 having the following formula:

5



wherein R^{20} , R^3 and R^5 are defined as

Cpd	R^{20}	R^3	R^5
3001		H	
3002		H	
3003		H	
3004		H	
3005		H	

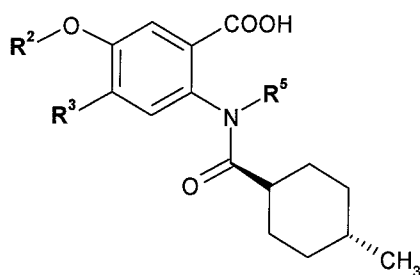
Cpd	R ²⁰	R ³	R ⁵
3006		H	
3007		F	
3008		F	
3009		F	
3010		F	
3011		F	
3012		F	
3013		F	

Cpd	R ²⁰	R ³	R ⁵
3014		F	
3015		F	

pharmaceutically acceptable salts or esters thereof.

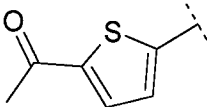
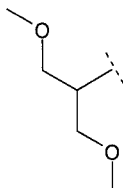
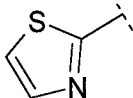
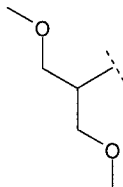
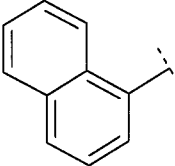
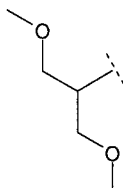
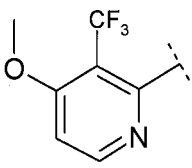
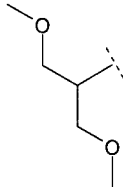
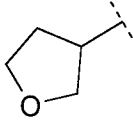
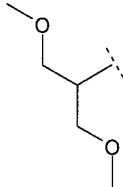
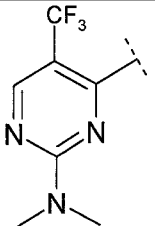
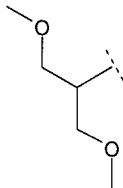
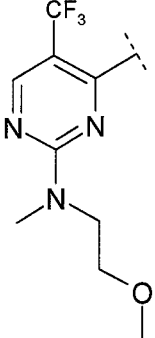
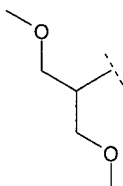
27. The compound according to claim 1 having the following formula:

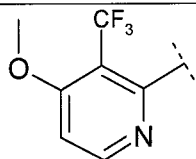
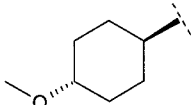
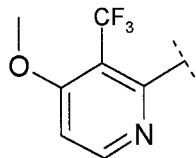
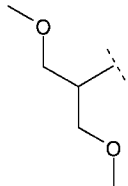
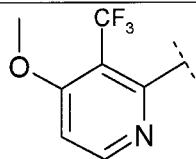
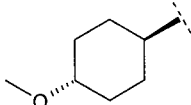
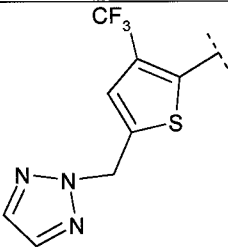
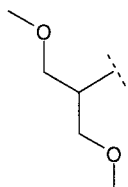
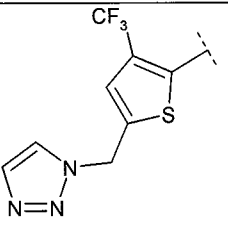
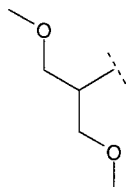
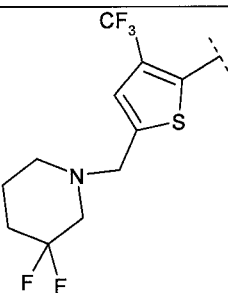
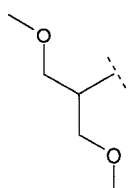
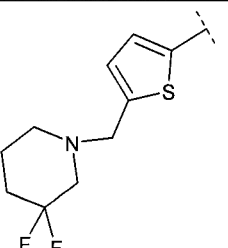
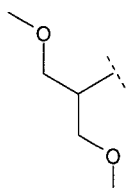
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wherein R², R³ and R⁵ are defined as:

Cpd	R ²	R ³	R ⁵
4001		F	
4002		H	
4003		H	

Cpd	R ²	R ³	R ⁵
4004		H	
4005		H	
4006		H	
4007		H	
4008		H	
4009		F	
4010		F	

Cpd	R ²	R ³	R ⁵
4011		F	
4012		F	
4013		H	
4014		H	
4015		H	
4016		H	
4017		H	

Cpd	R ²	R ³	R ⁵
4018		H	
4019		H	
4020		H	
4021		F	

pharmaceutically acceptable salts or esters thereof.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable carriers.

29. A pharmaceutical composition according to claim 28 additionally comprising at least one other antiviral agent.

- 15 **30.** The pharmaceutical composition according to claim 29 wherein the at least
one other antiviral agent comprises is selected from a NNRTI, NRTI, protease
inhibitor, HIV entry inhibitor and an integrase inhibitor.
- 20 **31.** Use of a pharmaceutical composition according to any one of claims 28 to 30
for the treatment of an HCV infection in a mammal having or at risk of having the
infection.
- 25 **32.** A method of treating an HCV infection in a mammal having or at risk of having
the infection, the method comprising administering to the mammal a therapeutically
effective amount of a compound according to any one of claims 1 to 27, a
pharmaceutically acceptable salt or ester thereof, or a composition according to any
one of 28 to 30.
- 30 **33.** A method of treating an HCV infection in a mammal having or at risk of having
the infection, the method comprising administering to the mammal a therapeutically
effective amount of a combination of a compound according to any one of claims 1
to 27 or a pharmaceutically acceptable salt or ester thereof, and at least one other
antiviral agent.
- 35 **34.** Use of a compound according to any one of claims 1 to 27, or a
pharmaceutically acceptable salt or ester thereof, for the treatment of an HCV
infection in a mammal having or at risk of having the infection.
- 40 **35.** Use of a compound according to any one of claims 1 to 27, or a
pharmaceutically acceptable salt or ester thereof, for the manufacture of a
medicament for the treatment of an HCV infection in a mammal having or at risk of
having the infection.
- 45 **36.** An article of manufacture comprising a composition effective to treat an HCV
infection; and packaging material comprising a label which indicates that the
composition can be used to treat infection by HCV; wherein the composition
comprises a compound according to any one of claims 1 to 27 or a pharmaceutically
acceptable salt or ester thereof.

37. A method of inhibiting the replication of HCV comprising exposing the virus to an effective amount of the compound according to any one of claims 1 to 27, or a salt or ester thereof, under conditions where replication of HCV is inhibited.

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38. Use of a compound according to any one of claims 1 to 39, or a salt or ester thereof, to inhibit the replication of HIV.